STUDIES AND SYNTHETIC APPLICATIONS OF THE O-STANNYL KETYL-PROMOTED CYCLOPROPANE FRAGMENTATIONS

By

ZHAOZHONG J. JIA

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To the memory of my grandfather

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STUDIES AND SYNTHETIC APPLICATIONS OF THE
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By

Zhaozhong J. Jia

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Chairman: Eric J. Enholm
Major Department: Chemistry

This dissertation investigated the O-stannyl ketyl-promoted cyclopropane fragmentations. O-stannyl ketyls were generated by the reactions of cyclopropyl ketones with tributyltin hydride or allyltributyltin. The goal of this study was to examine the reactivities of these cyclopropanes and examine the mechanistic attributes governing the cyclopropane fragmentation process, such as stereoelectronic effects and radical-stability effects. Another goal of this study was to apply the O-stannyl ketyl-promoted cyclopropane fragmentations to organic synthesis.

The first area of study was the O-stannyl ketyl-promoted cyclopropane fragmentations using tributyltin hydride. A variety of cyclopropyl ketone precursors were examined, including tricyclo[3.3.0.$0^{2,8}$]octan-3-one substrates. These fragmentations were governed by both stereoelectronic effects and radical-stability effects.

The second area of study was the synthetic applications of the O-stannyl ketyl-promoted cyclopropane fragmentations. The O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequence was accomplished. The efficient synthesis of two triquinane molecules demonstrated this tandem sequence and a novel synthetic methodology for triquinane compounds.

The third area of study included the preliminary work on the tin(IV) enolates generated in the cyclopropane fragmentations. Their applications in aldol and alkylation reactions were successful. Allyltributyltin-induced cyclopropane fragmentation-allylation reactions were also preliminarily examined.

CHAPTER 1
INTRODUCTION

The term "free radical" applies to a species possessing one unpaired electron.[1] A free radical is generated by homolytic cleavage of a covalent bond. The central atom is usually sp^2 hybridized and the unpaired electron resides in the *p*-orbital.[2] Though free radicals are highly reactive intermediates, reactions involving them generally embrace mild reaction conditions, in contrast to the harsh reaction conditions associated with the generation of cations or anions.

Free radical chemistry dates back to 1900 when Gomberg investigated the formation and reactions of triphenylmethyl radical.[3] However, free radicals had little synthetic use until the 1970s.[4] In that decade, new synthetic methods involving free radicals began to be developed. The understanding and synthetic applications of radicals have grown quickly since. Today free radical reactions have been a routine method to accomplish constructions of a wide variety of carbon and hetereoatom skeletons.[5]

Organotin compounds have been extensively studied for decades.[6] Among them, tributyltin hydride (TBTH) has been known for over 30 years to engage in free radical reactions. It is commercially available and can be readily prepared as well.[6,7] Tin has a $5s^25p^2$ electronic configuration and exists in tetrahedral sp^3 hybridization in TBTH. The Sn-H bond in TBTH is of 0.17 nm in length and 73.7 kcal/mol in bond dissociation energy (BDE).[6d,g,8] This bond can be homolytically-cleaved with a radical initiator to produce a tributyltin

radical. Azo and peroxide compounds are common free radical initiators, possessing a weak C-N bond or O-O bond, as shown in Figure 1-1.[2a]

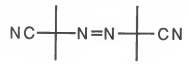
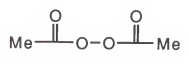
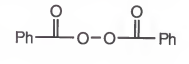
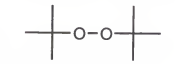
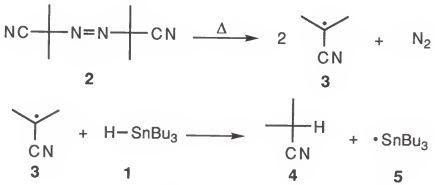
Name	Structure	BDE (kcal/mol)	Temperature for 1-hr Half-life (°C)
AIBN		30	85
acetyl peroxide		30-32	85
benzoyl peroxide		30	95
t-butyl peroxide		37	150

Figure 1-1
Common free radical initiators

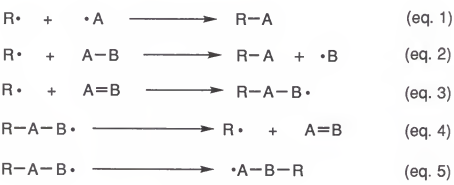
The combination of TBTH **1** and initiator AIBN (azobisisobutylnitrile) **2** in refluxing benzene (80°C) is the most popular way to generate tributyltin radical. As shown in Scheme 1-1, thermal decomposition of AIBN produces cyanoisopropyl radical **3**, which abstracts a hydrogen atom from the Sn-H bond



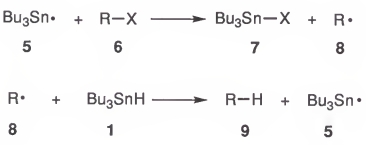
Scheme 1-1

of TBTH to give tributyltin radical **5**.

There are five broad classes of free radical reactions,[9] as shown in Scheme 1-2: i) radical combination (coupling) (eq. 1); ii) radical abstraction of an atom or group (eq. 2); iii) radical addition to a multiple bond (eq. 3); iv) radical fragmentation (β-elimination), the reverse process of addition (eq. 4); v) radical rearrangement (eq. 5).



Scheme 1-2

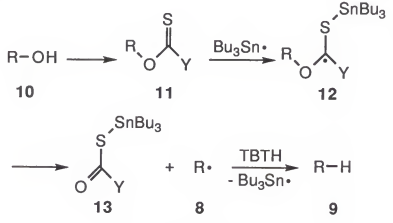


Scheme 1-3

The atom or group abstraction reactions (eq. 2) of tributyltin radicals are very useful. Halide abstraction is of great synthetic importance.[6g] Bromide and iodide are most commonly used. As shown in Scheme 1-3, halide reduction occurs through a chain mechanism. Tributyltin radical **5** abstracts halogen atom X from halide **6**, generating carbon-centered radical **8**. Radical **8** abstracts a hydrogen atom from TBTH, giving reduction product **9** and another tributyltin

radical to carry on this chain reaction. Depending on its structure, radical intermediate **8** may undergo addition, fragmentation or rearrangement reactions before the final hydrogen abstraction occurs.

TBTH reduces thiols, thioethers and selenides as well, due to the formation of strong Sn-S or Sn-Se bonds.[6g] Barton developed this reduction into a powerful deoxygenation method,[10] which can be applied to a wide variety of hydroxy compounds, including primary, secondary, tertiary alcohols and diols. The general sequence of a Barton deoxygenation is shown in Scheme 1-4. This reaction proceeds through an addition of tributyltin radical to the thiocarbonyl group, followed by fragmentation of carbon-centered radical **12** to liberate alkyl radical **8** and restore the carbonyl function. Radical **8** abstracts a hydrogen atom from TBTH, giving reduction product **9**. The Y group can be hydrogen, methyl, phenyl, S-methyl, S-phenyl, O-phenyl and imidazolyl.[6g]



Scheme 1-4

The addition of a free radical to a multiple bond constructs a new σ-bond at the cost of a π-bond, as shown by eq. 3 in Scheme 1-2. Though this addition is energetically favorable, it is still considered reversible. The rate of this radical addition is influenced by the stabilities of R•, multiple bond A=B, and radical

RAB• formed by the addition; steric hindrance to the addition step; and polar factors.[2a] The substituents on R• and on the multiple bond play important roles in this addition. These substituent effects can be understood through the frontier molecular orbital (FMO) theory.[11,12]

In the FMO theory, patterns of reactivity can often be addressed in terms of interactions between the FMOs in the two reacting species. The FMO of a free radical is its "singly occupied" molecular orbital (SOMO). The FMOs of a multiple bond are its "highest occupied" molecular orbital (HOMO) and "lowest unoccupied" molecular orbital (LUMO).[12] A very important determinant of the activation energy of this reaction is the SOMO-HOMO and SOMO-LUMO interactions. Since orbital interaction is stronger for orbitals of comparable energy, one of these two interactions is usually more significant than the other if the SOMO-HOMO energy gap and the SOMO-LUMO energy gap are not equal. Any substituent on either the radical or the multiple bond lowering the SOMO-HOMO or SOMO-LUMO energy gap lowers the activation energy of this addition.[11,12]

The electronic characteristics of radicals and multiple bonds are defined as the following. An "electrophilic" radical, possessing an electron-withdrawing-group (EWG) substituent, has an energy-lower SOMO. A "nucleophilic" radical, possessing an electron-donating-group (EDG) substituent, has an energy-higher SOMO. An "electron-rich" multiple bond, possessing an EDG, has an energy-higher HOMO. An "electron-deficient" multiple bond, possessing an EWG, has an energy-lower LUMO.[12]

A favorable SOMO-HOMO or SOMO-LUMO interaction is required for a radical addition reaction to occur, as shown in Figure 1-2. For an electrophilic radical (low SOMO), its interaction with the HOMO is usually more significant than that with the LUMO. For a nucleophilic radical (high SOMO), the SOMO-

LUMO interaction is usually stronger than the SOMO-HOMO interaction.[11] Alkyl radical is nucleophilic, and its interaction with a receiving multiple bond is thus mainly in a SOMO-LUMO manner.

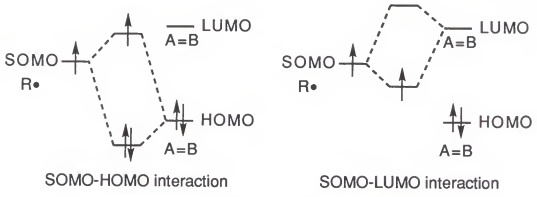
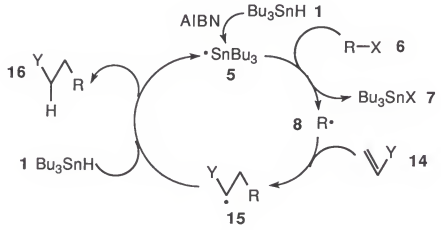


Figure 1-2
Orbital interactions of a radical with a multiple bond (eq. 3)

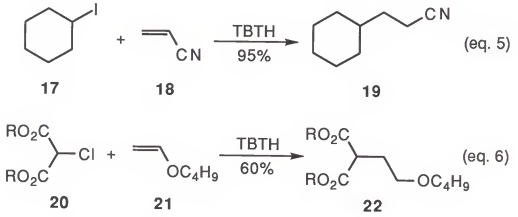


Scheme 1-5

Formation of carbon-carbon bonds is the heart of organic synthesis. With a new carbon-carbon bond constructed, the addition of an alkyl radical to an alkene or alkyne is synthetically important.[1] For this radical intermolecular addition to be successful, a selectivity requirement must be fulfilled. This requirement pertains to intermediates **5**, **8**, and **15** (Scheme 1-5).[1] Each

intermediate should have a specific partner to react with. If **8** and **15** have the same tendency to add to alkene **14**, polymerization can result. To prevent polymerization, the electronic characteristics of **8** and **15** must be opposite in nature so that they have different reactivities towards alkene **14**.

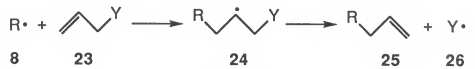
To fulfill the selectivity requirement, a combination of nucleophilic alkyl radical **8** and electron-deficient alkene **14** (Y=EWG) is popular.[13] Nucleophilic **8** readily reacts with **14**, producing electrophilic **15**. This radical does not react with electron-deficient **14** and will eventually be quenched by TBTH to give **16**. The reaction of eq. 5 (Scheme 1-6) is such an example. Alkene **18** is electron-deficient, due to the cyano group. Under TBTH treatment iodide **17** provides nucleophilic cyclohexyl radical. However, the combination of electrophilic **8** and electron-rich **14** (Y=EDG) works well too. As shown in eq. 6, **21** is electron-rich, and electrophilic radical is generated from chloride **20**.



Scheme 1-6

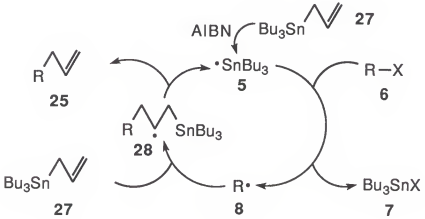
After a new carbon-carbon bond forms in an addition, adduct radical **26** can be transformed into a non-radical product not only by a hydrogen abstraction from TBTH, but also by homolytically cleaving a β-bond to split off radical **26**, as shown in Scheme 1-7.[1] This fragmentation prevents radical **24**

from reacting with alkene **23**. If this β-elimination is fast enough, radicals **8** and **24** need not to be of different electronic characteristics.

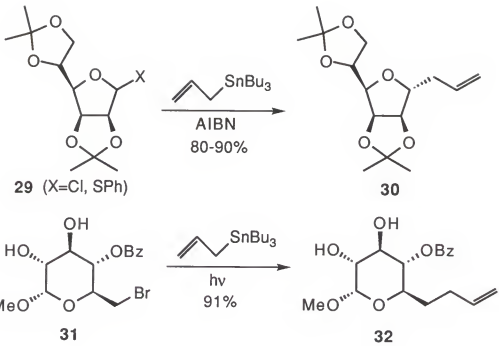


Scheme 1-7

Keck's allylation reactions involve such a β-elimination.[14] Keck used allyltributyltin **27** to intermolecularly accept alkyl radical **8**, as shown in Scheme 1-8. Once adduct **28** forms, the C-Sn bond β to the radical center rapidly fragments, giving tributyltin radical **5** and allylated product **25**. Radical **5** then abstracts the X group from **6**, reproducing alkyl radical **8** to renew the reaction cycle. Substrate **6** can be a halide, thioether, selenide or xanthate. A variety of substrates **6**, including carbohydrate derivatives, can be applied (Scheme 1-9).[14]

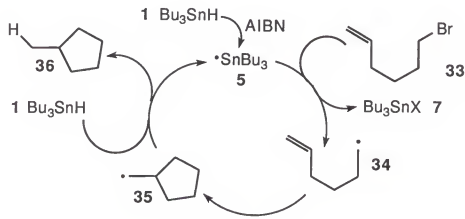


Scheme 1-8



Scheme 1-9

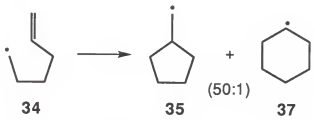
"Cyclizations" are intramolecular additions. A typical 5-hexenyl radical cyclization is shown in Scheme 1-10.[1] The cyclization rate constant of 5-hexenyl radical **34** to cyclopentylmethyl radical **35** is about 10^5 s^{-1} at 25°C. It



Scheme 1-10

can be further increased by making the alkene electron-deficient with an EWG substituent.[15] Although radicals **34** and **35** have the same nucleophilicity, the selectivity requirement for chain reactions can still be fulfilled: **34** cyclizes to the alkene, whereas **35** only reacts with TBTH in an intermolecular manner.

Free radical cyclizations are powerful methods for five- and six-membered ring constructions. Molecular geometry is a key factor to influence the regioselectivity and stereochemistry of the cyclizations. The cyclizations of 5-hexenyl radical **34** have been extensively studied and proceed in a highly regioselective manner.[16,17] In almost all cases, 5-hexenyl radicals preferentially engage in 5-exo cyclizations, following Baldwin's rule.[18] The 5-exo cyclization product **35** forms faster than the 6-endo product **37** in a ratio of 50:1, as shown in Scheme 1-11.[16]



Scheme 1-11

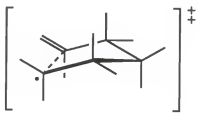
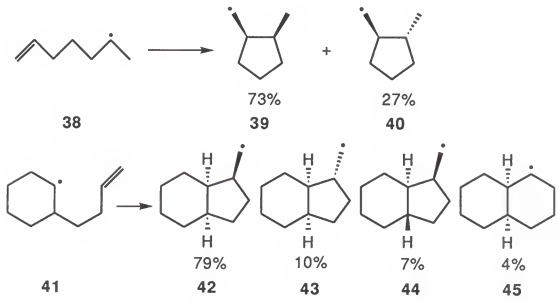


Figure 1-3
Beckwith's chair transition state for 5-hexenyl radical cyclization

According to Beckwith, 5-hexenyl radical cyclization proceeds through a chair-like transition state (Figure 1-3), with substituents preferring pseudo-

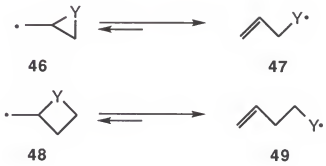
equatorial positions on the six-membered ring.[16] The stereochemistry of the major cyclization product is determined by this chair-like transition state, as demonstrated by the examples in Scheme 1-12.[1]



Scheme 1-12

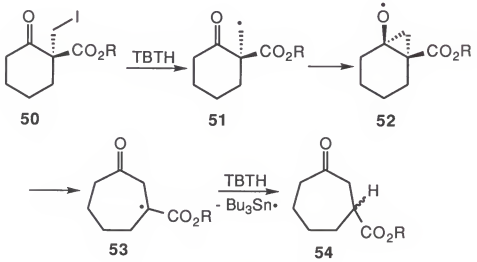
"Fragmentation" is the reverse process of an addition. The β-elimination of tributyltin radical in Keck's allylation (Scheme 1-8) is a radical fragmentation. A new radical and a new multiple bond are generated in the homolytic cleavage of a σ-bond. The cleavage of an adjacent strained ring, such as a cyclopropane, cyclobutane or epoxide, is a special type of radical fragmentation, as shown in Scheme 1-13. The strain energy in a simple cyclopropane is 28.3 kcal/mol, while that in a simple cyclobutane is 27.4 kcal/mol and that in a simple epoxide is 27.2 kcal/mol.[19] Though these free radical ring cleavage and closure processes are considered reversible, the ring cleavage occurs at a much higher rate to release ring strains.[1,15a,b] For example, the rate constant for ring opening of cyclopropylcarbinyl radical **46** (Y=CH_2) to allylcarbinyl radical **47**

($Y=CH_2$) is $1.3 \times 10^8\ s^{-1}$ at 25°C, while the rate constant for the reverse process is only $4.9 \times 10^3\ s^{-1}$.[15a]



Scheme 1-13

A simple strained-ring fragmentation is of limited synthetic importance. However, when this fragmentation couples with another free radical reaction, a variety of tandem sequences can result.[20]

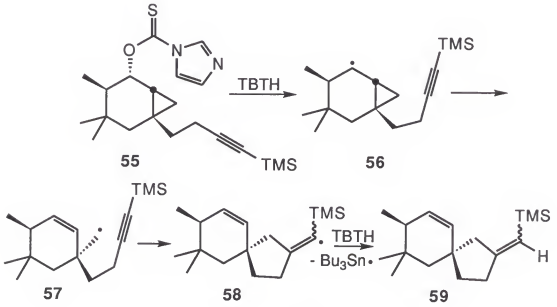


Scheme 1-14

Dowd demonstrated an interesting "cyclization-fragmentation" tandem sequence, as shown in Scheme 1-14.[21] In this process, radical **51** first adds to

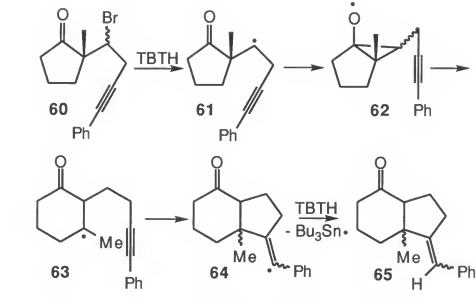
the carbonyl, giving cyclopropane **52**. Due to the ring strain, this cyclopropane is unstable and fragments to afford ester-stabilized radical **53**, which abstracts a hydrogen from TBTH to give **54** and a tributyltin radical to renew the reaction cycle. This sequence expands cyclohexanone **50** to cycloheptanone **54**.

A free radical "fragmentation-cyclization" sequence was accomplished by Motherwell, as shown in Scheme 1-15.[22] Radical **56** cleaves the adjacent cyclopropane, giving radical **57** which cyclizes onto an alkyne ether to construct a spiro ring skeleton. Vinyl radical **58** reacts with TBTH to abstract a hydrogen atom in the final step.

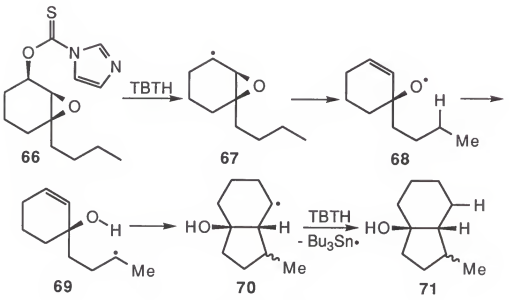


Scheme 1-15

Boger realized a radical "cyclization-fragmentation-cyclization" tandem sequence, as shown in Scheme 1-16.[23] Unstable cyclopropane intermediate **62** first forms through a radical cyclization onto the carbonyl. The cyclopropane fragments to produce tertiary radical **63** which is captured by an alkyne tether in the following 5-exo-dig cyclization.



Scheme 1-16

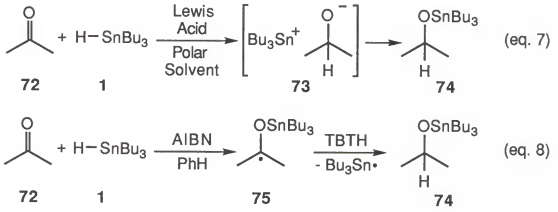


Scheme 1-17

Free radical-induced epoxide fragmentation offers a convenient method to generate reactive oxygen-centered radicals.[1] This epoxide fragmentation also can be used in synthetically useful tandem sequences, as demonstrated in Scheme 1-17.[24] A radical is generated α to epoxide in **67**. The epoxide's C-O

bond selectively cleaves, giving oxygen-centered radical **68**. Through a 1,5-hydrogen migration, radical **68** intramolecularly abstracts a hydrogen atom, affording carbon-centered radical **69**. Radical **69** cyclizes onto the olefin to produce bicycle **70**.

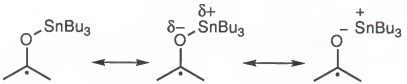
TBTH reduces aldehydes and ketones to alcohols.[6g] Depending on reaction conditions, two different mechanisms are postulated for the initial hydrostannation step of the reduction, as shown in Scheme 1-18.[6g] When polar solvent and Lewis acid catalyst are used, the ionic pathway dominates (eq. 7). In this mechanism, TBTH acts as a hydride donor, giving intermediate **73** which reorganizes to afford tin alkoxide **74**. The tin moiety is subsequently released by hydrolysis with water, alcohols or acids, yielding alcohol.



Scheme 1-18

A free radical pathway is postulated when the combination of TBTH and AIBN in benzene is used (eq. 8).[6g] O-stannyl ketyl radical **75** initially forms through the addition of oxophilic tributyltin radical to carbonyl **72**. This carbon-centered ketyl radical **75** abstracts a hydrogen from TBTH, producing tin alkoxide **74** and regenerating tributyltin radical to renew the reduction process. Alcohol product is obtained by hydrolysis of **74**.

The chemistry of O-stannyl ketyls is the focus of this dissertation. An O-stannyl ketyl can be viewed as a pseudo-protected radical anion, because the O-Sn bond has a certain degree of ionic character, due to the electronegativity difference between oxygen and tin (Scheme 1-19). The early investigations of this chemistry in the 1970s were mainly concentrated on mechanistic studies of the O-stannyl ketyl-promoted fragmentations of simple cyclopropyl ketones and α,β-epoxyketones.[6g,25] It was not until the mid-1980s when chemists finally began to examine O-stannyl ketyls for a synthetic purpose.

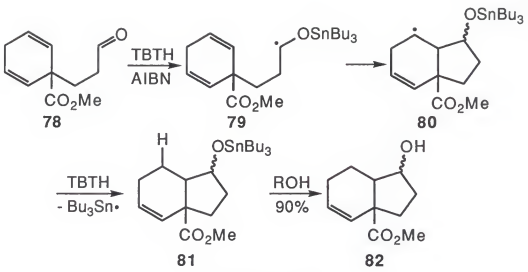


75 **76** **77**

Scheme 1-19

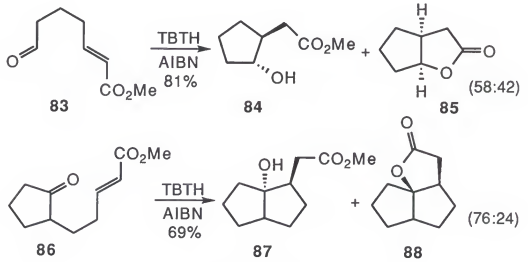
The year 1985 welcomed the earliest synthetic work on O-stannyl ketyls. Tanner performed a series of investigations to study ketone reduction by organotin hydrides.[26] O-stannyl ketyl-promoted cyclopropane fragmentations were once again examined using cyclopropyl phenyl ketone. Rahm studied the effect of high pressure on ketone reduction by TBTH, including cyclopropyl ketones and α,β-epoxyketones.[27]

In 1986, Beckwith accomplished the cyclization of O-stannyl ketyl onto a multiple bond, as shown in Scheme 1-20.[28] Though the yield was excellent, this reaction was sluggish and required excess TBTH. It took 40 hours for the cyclization to complete. Similar O-stannyl ketyl cyclizations were reported by Julia (1987) and by Ueda (1988).[29,30]



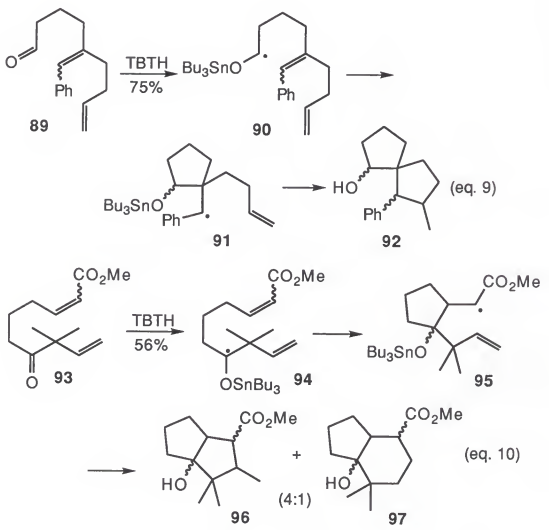
Scheme 1-20

Enholm has been actively engaged in the synthetic studies of O-stannyl ketyls since 1989.[31-37] He envisioned that the cyclization of nucleophilic O-stannyl ketyl would be much faciliated if the ketyl-accepting multiple bond was electron-deficient.[31] Enholm demonstrated that aldehydes and ketones could readily cyclize onto tethered olefinic appendages under treatment of TBTH and



Scheme 1-21

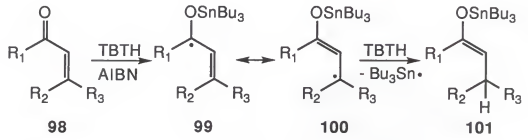
AIBN, as shown in Scheme 1-21.[31] Both 5-exo and 6-exo cyclizations of olefins "activated" by an EWG substituent, such as an ester, nitrile or phenyl, were achieved.



Scheme 1-22

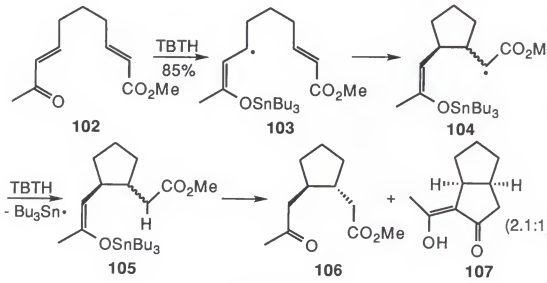
Enholm realized O-stannyl ketyl-promoted tandem radical cyclizations.[32] He synthesized spiro (eq. 9) and fused (eq. 10) bicycles, as shown in Scheme 1-22. Activated olefin engaged in the first cyclization. Nucleophilic O-stannyl

ketyl radical cyclized onto this electron-deficient olefin, affording electrophilic radical (**92** and **95**) which cyclized onto the electron-rich olefin tether.



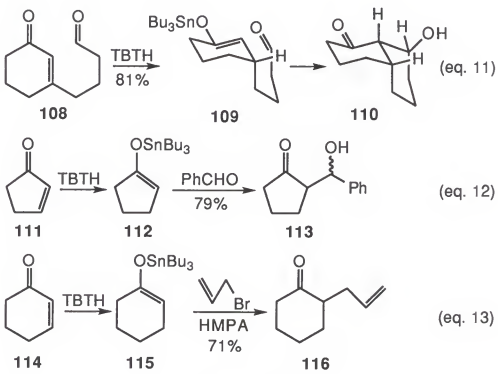
Scheme 1-23

Enholm examined allylic O-stannyl ketyls **99**, produced by the reaction of α,β-unsaturated carbonyls with TBTH, as shown in Scheme 1-23.[33,34] Allylic ketyl radical **99**, once generated, enjoys resonance with the adjacent olefin moiety to give **100**, a combination of tin(IV) enolate and free radical. Enholm demonstrated that this free radical could be intramolecularly captured by an olefin tether, as shown in Scheme 1-24.[33]



Scheme 1-24

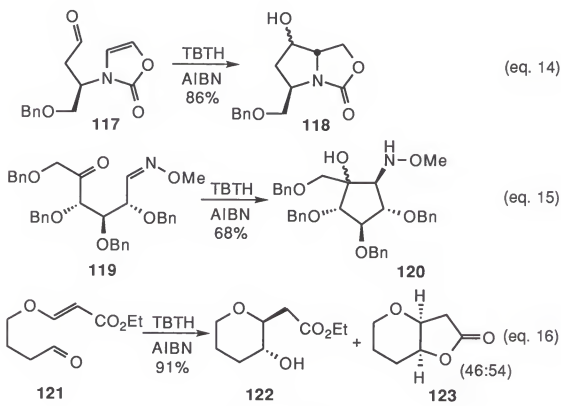
Enholm discovered that for allylic O-stannyl ketyls, after free radical **100** was quenched by a hydrogen abstraction from TBTH, tin(IV) enolate **101** could undergo a variety of interesting reactions, including intramolecular (eq. 11) and intermolecular (eq. 12) aldol condensation and alkylation reactions (eq. 13), as shown in Scheme 1-25.[34] These observations are in direct contrast to how an α,β-unsaturated ketone is normally viewed in free radical reactions, where it often functions as electron-deficient radical acceptor in a 1,4-addition manner.



Scheme 1-25

O-stannyl ketyls are suitable for cyclizations with hetereoatom-substituted carbon-carbon double bonds or carbon-nitrogen double bonds, demonstrated first by Ueda in 1988.[30] Kim observed O-stannyl ketyl cyclization onto imine.[38] Shibuya achieved cyclization with oxazolidinone as the ketyl acceptor (eq. 14, Scheme 1-26).[39] Naito reported cyclization of O-stannyl ketyl with oxime ether

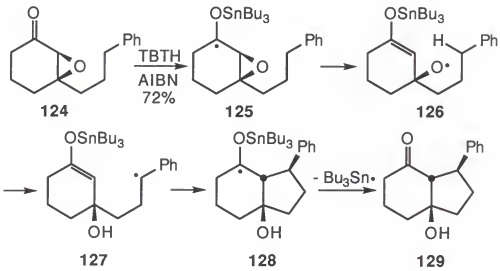
119 (eq. 15).[40] Lee found that β-alkoxyacrylate **121** was an efficient ketyl acceptor, and accomplished the synthesis of fused oxacycle **123** (eq. 16).[41]



Scheme 1-26

The 1990s witnessed the reinvestigation of O-stannyl ketyl-induced epoxide fragmentations. Hasegawa reported the selective C-O bond cleavage of α,β-epoxy ketones by thermal and photochemical reactions with TBTH.[42] Bowman studied the epoxide fragmentation in 2-ketobicyclo[2.2.1]heptan-3-spiro-2'-oxirane substrates and reached the same conclusion.[43] Rawal and Kim accomplished an interesting tandem sequence using this fragmentation, as shown in Scheme 1-27.[44] Similar to that in Scheme 1-19, this sequence started from selective cleavage of the epoxide's C-O bond, giving reactive oxygen-centered radical **126**, which promoted a 1,5-hydrogen abstraction and

a radical cyclization. Tributyltin radical was ejected from rearranged O-stannyl ketyl **128** to restore the original carbonyl function.



Scheme 1-27

Free radicals have been among the most extensively used intermediates in organic synthesis.[5] Unfortunately, O-stannyl ketyl is much less studied and still poorly understood. As pointed out before, although the O-stannyl ketyl-promoted cyclopropane fragmentation has been known for over 25 years,[25] this reaction was only examined using simple molecules for mechanistic interests. No synthetic application of this fragmentation had ever been reported prior to the work described in this dissertation. In order to continue the exploration and understanding of O-stannyl ketyls, this dissertation investigates the O-stannyl ketyl-promoted cyclopropane fragmentations with a wide variety of substrates. This dissertation demonstrates a novel O-stannyl ketyl-initiated cyclopropane fragmentation-cyclization tandem sequence and applies it to the efficient synthesis of two triquinane molecules. This dissertation also examines the chemistry of tin(IV) enolates, produced in cyclopropane fragmentations.

Chapter 2 describes the studies of O-stannyl ketyl-promoted cyclopropane fragmentations using simple, bicyclic and tricyclic substrates. A special tricyclic substrate, tricyclo[3.3.0.$0^{2,8}$]octan-3-one, was treated with TBTH to produce different ring cleavage products, depending on the location and type of substituent present. An examination of both radical-stabilizing substituents and stereoelectronic effects was carried out to understand which factors biased the bond cleavage in a rigid α-ketocyclopropane.

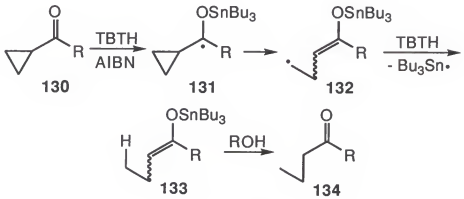
Chapter 3 examines the tandem sequence arising from O-stannyl ketyl-promoted cyclopropane fragmentation and following radical cyclization. This radical tandem sequence gave high yields in good stereoselectivity. This work accomplished the novel synthesis of an angular and a linear triquinane model compound. This is the first ever known example of the O-stannyl ketyl-initiated cyclopropane fragmentation-cyclization tandem reactions.

Chapter 4 demonstrates the applications of tin(IV) enolates generated in cyclopropane fragmentations. These tin(IV) enolates could engage in aldol condensation and alkylation reactions. Chapter 4 also examines the allyltributyltin-induced cyclopropyl ketone fragmentation-allylation.

The viability of free radicals as powerful synthetic intermediates has been well proved.[5] Free radicals are generated under mild and neutral conditions, tolerate a wide range of functionalities, and usually react regioselectively and stereoselectively. O-stannyl ketyl radicals possess unique attributes in organic synthesis. The work described in this dissertation broadens the knowledge of this special ketyl species. O-stannyl ketyl-promoted cyclopropane fragmentation produces a free radical along with a regiospecific tin(IV) enolate. This work individually manipulates these two intermediates. Further efforts to take advantage of them both will definitely lead to exciting developments.

CHAPTER 2
STUDIES OF THE O-STANNYL KETYL-PROMOTED
CYCLOPROPANE FRAGMENTATIONS

The origin of this work was the mechanistic studies of the O-stannyl ketyl-promoted cyclopropane fragmentations in the early 1970s by Godet and Pereyre.[25a,b,c] They found that under free radical conditions, the reaction of cyclopropyl ketone **130** with TBTH gave cyclopropane scission product **134**, as shown in Scheme 2-1. In this reaction, the carbonyl was first reduced to O-stannyl ketyl **131**, which cleaved the adjacent cyclopropane. Radical product **132** was reduced by hydrogen abstraction from TBTH, giving tin(IV) enolate **133** and reproducing tributyltin radical to carry on the chain process. Enolate **133** was finally hydrolyzed to **134**. This fragmentation mechanism was confirmed later by other independent studies.[25-27]

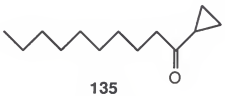


Scheme 2-1

O-stannyl ketyl-promoted cyclopropane fragmentations are synthetically valuable. At the expense of a cyclopropyl ketone, an alkyl radical and a tin(IV)

enolate are produced. Although the original investigators did not explore either, both the radical and tin(IV) enolate are useful intermediates in organic synthesis. Cyclopropyl ketone **130** can be readily prepared by a variety of methods, such as using an α,β-unsaturated ketone and sulfur ylide,[45] or cyclopropanating an allylic alcohol and then oxidizing the product,[46] or cyclopropanating an alkene with a diazo function and a transition metal catalyst intramolecularly or intermolecularly.[47]

The synthetic applications of the O-stannyl ketyl-promoted cyclopropane fragmentations had not been known prior to the work described in this dissertation. Inspired by Motherwell's free radical cyclopropane fragmentation-cyclization tandem sequence (Scheme 1-15),[22] we planned to examine this sequence promoted by O-stannyl ketyl.



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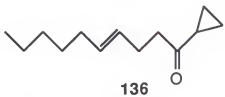

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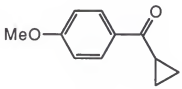

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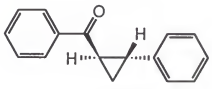
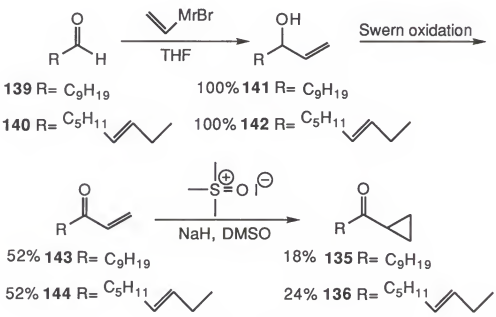


138

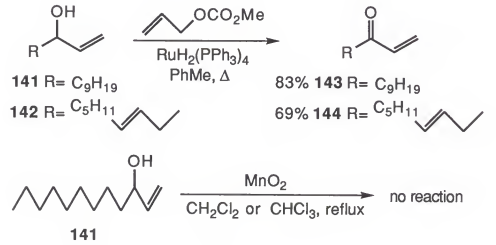
Figure 2-1
The simple cyclopropyl ketones for the fragmentation studies

To initiate our investigation of the O-stannyl ketyl-promoted cyclopropane fragmentations, four simple cyclopropyl ketones, shown in Figure 2-1, were planned. The preparation of substrates **135** and **136** was first planned as that shown in Scheme 2-2, starting from commercial aldehydes **139** and **140**. Addition of vinyl Grignard to the aldehydes gave allylic alcohols **141** and **142**

in quantitative yields. Swern reaction was used to oxidize the alcohols to vinyl ketones **143** (52%) and **144** (52%).[48] Sulfur ylide method was employed to produce cyclopropyl ketones **135** (18%) and **136** (24%) in modest yields.[45]



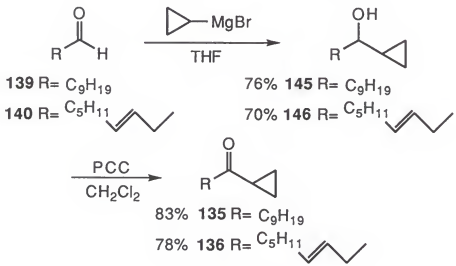
Scheme 2-2



Scheme 2-3

To improve the yields, a ruthenium-catalyzed oxidation method with allyl methyl carbonate was used,[49] affording vinyl ketones **143** (83%) and **144** (69%), as shown in Scheme 2-3. MnO_2 oxidation was attempted as well.[50] However, no oxidation was observed, even when the reaction mixture in chloroform was refluxed.

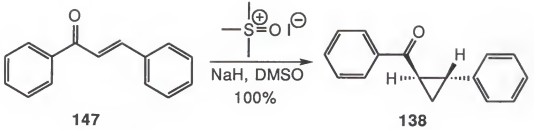
The preparation of cyclopropyl ketones **135** and **136** was also achieved by an alternative route shown in Scheme 2-4. The Grignard reagent of cyclopropyl bromide reacted with aldehydes **139** and **140**, providing cyclopropyl alcohols **145** (76%) and **146** (70%). Pyridinium chlorochromate (PCC) oxidized them to desired substrates **135** (83%) and **136** (78%).



Scheme 2-4

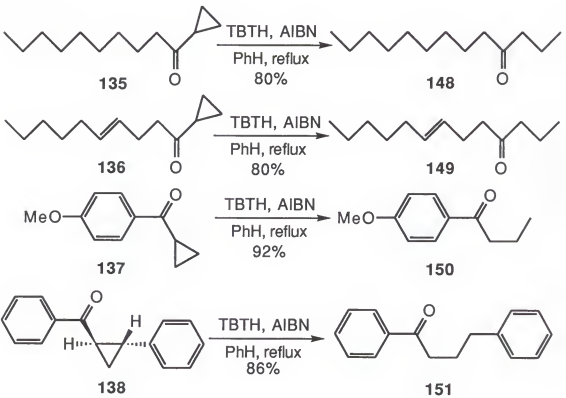
Cyclopropyl ketone **137** was commercially available. The preparation of substrate **138** was accomplished in quantitative yield from *trans*-chalcone **147** with sulfur ylide,[45] as shown in Scheme 2-5.

The O-stannyl ketyl-promoted cyclopropane fragmentations of these simple substrates occurred readily in refluxing benzene, giving cyclopropane-scission products in good yields, as shown in Scheme 2-6.



147 138

Scheme 2-5

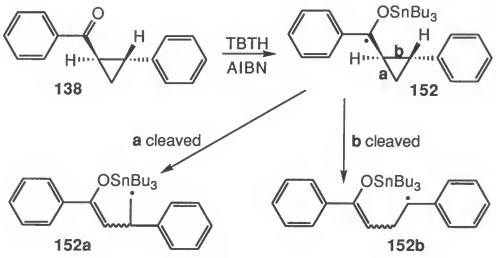


135 148
136 149
137 150
138 151

Scheme 2-6

For phenyl-substituted cyclopropane **138**, its two C^{α}-C^{β} cyclopropane bonds (bond **a** and bond **b**) were not identical. When this cyclopropane fragmented, two products **152a** and **152b** could form, as shown in Scheme 2-7. Secondary radical **152b** is strongly stabilized by a phenyl substituent and is therefore much more stable than primary radical **151a**. Because the cyclopropane rotated freely, bonds **a** and **b** had the same orbital overlap with

the sp^2-like orbital of ketyl radical **152**. Thus, stereoelectronic influences were absent in this fragmentation.[51] As a result, this fragmentation was controlled by radical-stability effects, selectively yielding **151**.



Scheme 2-7

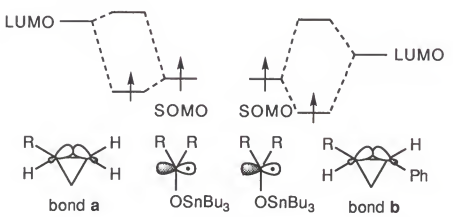


Figure 2-2
SOMO-LUMO interactions of O-stannyl ketyl with cyclopropane in **152**

A second way to understand the cyclopropane fragmentation of ketyl **152** was through Mariano's FMO theory.[12,25k] A favorable interaction between the SOMO of O-stannyl ketyl (bearing electron-donating $OSnBu_3$) and the

LUMO of a cyclopropane σ-bond is required for its cleavage to occur. A cyclopropane σ-bond substituted with an EWG has a lower energy LUMO, whereas that substituted with an EDG has a higher energy LUMO. For cyclopropane **152**, bond **b** carried EWG phenyl and had a lower LUMO than bond **a**. Since stereoelectronic influences were absent, a better interaction was achieved between the ketyl's SOMO and **b**'s LUMO, as shown in Figure 2-2. Thus, **b** cleavage was favored in this freely-rotating cyclopropane substrate.

To study the O-stannyl ketyl-promoted fragmentation of a cyclopropane fused in bicyclic or tricyclic systems, three such substrates (**153**, **154** and **155**) were planned, as shown in Figure 2-3.

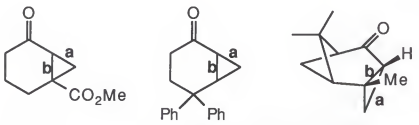
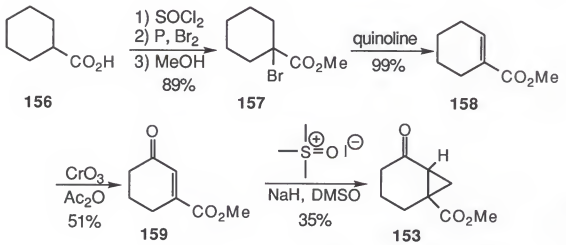


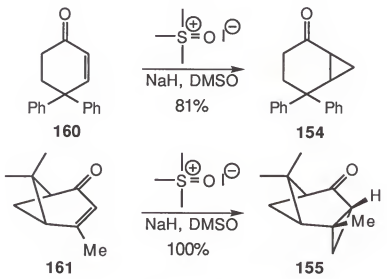
Figure 2-3
The bicyclic and tricyclic substrates



Scheme 2-8

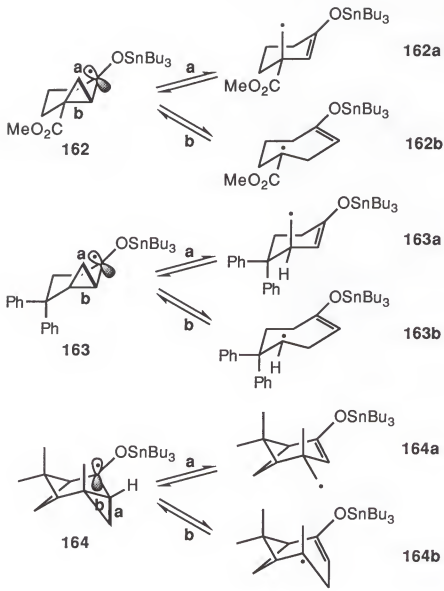
The preparation of **153** is shown in Scheme 2-8. The synthetic route to **159** followed Lange's procedure.[52] Conversion of **156** to **157** was achieved in 89% yield by Hell-Volhard-Zelinsky reaction. Dehydrobromination of **157** in quinoline gave **158** in quantitative yield. Allylic oxidation with chromium(VI) trioxide produced **159** in 51% yield. Sulfur ylide reaction transformed **159** to **153** in 35% yield.[45]

Substrates **154** and **155** were prepared from commercial α,β-unsaturated ketones **160** and **161** using sulfur ylides,[45] as shown in Scheme 2-9.



Scheme 2-9

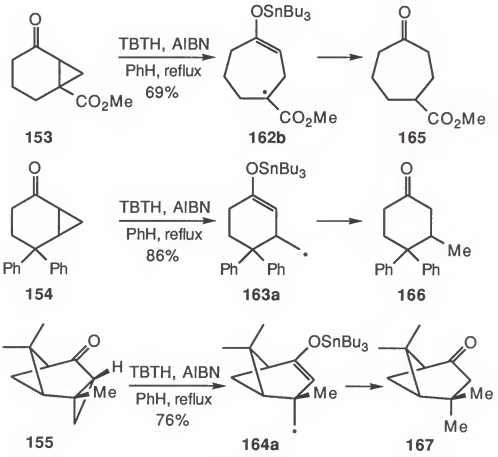
Bicyclic and tricyclic substrates **153**, **154** and **155** possess a rigidly fused cyclopropane. Stereoelectronic requirements of orbital overlap are expected to govern these cyclopropane fragmentations. For each substrate, once O-stannyl ketyl forms, its sp^2-like orbital has better overlap with bond **a**. Bond **b**, conversely, is almost orthogonal to this sp^2-like orbital, as illustrated in Scheme 2-10.[53,54]



Scheme 2-10

On the basis of stereoelectronic effects,[51] bond **a** cleavage should predominate over bond **b** cleavage, and the **a** cleavage products (**162a**, **163a** and **164a**) should predominate in the fragmentations. For O-stannyl ketyl **162**, stereoelectronic effects compete with radical-stability effects which favor bond **b** cleavage, due to the stabilization of **162b** by the ester. Intermediate **162a** may form kinetically, but the more stable ring-enlarged **162b** would eventually

predominate in the equilibrium, because of the reversibility of cyclopropane fragmentation.[55] Thus, ring expansion could occur for substrate **153** under treatment of TBTH and AIBN.

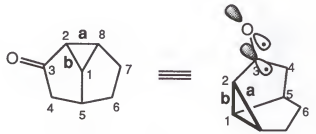


Scheme 2-11

To examine if stereoelectronic effects or radical-stability effects would predominate in the cyclopropane fragmentations, the reactions of substrates **153**, **154** and **155** with TBTH and AIBN were performed. As shown in Scheme 2-11, for ester-substituted cyclopropane **153**, ring expansion product **165** (69%) was exclusively yielded, revealing predominance of **162b** in the fragmentation. Radical-stability effects overcame stereoelectronic effects for this substrate and bond **b** was selectively cleaved. For substrates **154** and **155**,

bond **a** cleavage predominated and stereoelectronic effects-favored products **166** (86%) and **167** (76%) were yielded. Apparently, the driving force for more stable bond **b**-scission products **163b** and **164b** was not sufficient enough to compete with stereoelectronic effects. Thus, it was clear that the significance of radical-stability effects mainly depended on the substitution pattern of the cyclopropane. An ester or similar radical-stabilizing group at the cyclopropane's Cβ position was required for radical-stability effects to predominate. Recently, Cossy reached a similar conclusion by studying the photochemical electron transfer-induced ring scission of cyclopropyl ketones.[54]

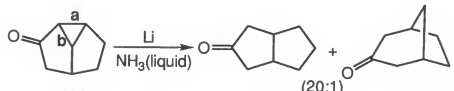
A unique cyclopropyl ketone, tricyclo[3.3.0.0^{2,8}]octan-3-one **168** (Figure 2-4), strongly held our attention and curiosity.[35] Containing a geometrically defined α-ketocyclopropane component rigidly fused on parent diquinane, **168** was perfect for examining the competition of stereoelectronic effects and radical-stability effects in O-stannyl ketyl-promoted cyclopropane scissions. Stereomodels of **168** showed that the π-bond of the carbonyl forms a dihedral angle of approximately 25° with the C2-C8 σ-cyclopropane bond **a**.[56] Bond **a** is geometrically disposed for better overlap with the adjacent π-system than the C1-C2 σ-cyclopropane bond **b**.



168

Figure 2-4
Tricyclo[3.3.0.0^{2,8}]octan-3-one

Metal-associated ketyl-mediated cyclopropane fragmentation of **168** was investigated by Monti in 1969, using harsh lithium-liquid ammonia medium, as shown in Scheme 2-12.[56] Stereoelectronic effects governed this ring scission. The overall two-electron reduction selectively cleaved bond **a**, giving **169** and **170** in a ratio of 20 to 1.



168 **169** **170**

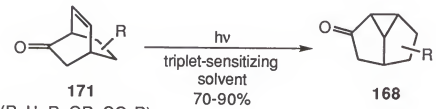
Scheme 2-12

The examination of this cyclopropane fragmentation using TBTH and AIBN was planned. Prior to the work presented in this dissertation, it had not yet been clear whether O-stannyl ketyl would behave in an analogous manner. This O-stannyl ketyl-promoted fragmentation markedly differed from the lithium-ammonia redox process in mechanism. O-stannyl ketyl reacted by free radical pathway under mild conditions, relative to the dissolved metal reduction.

The special merit of tricyclo[3.3.0.0^{2,8}]octan-3-one **168** in the synthesis of cyclopentanoid natural products was recognized in 1980 by Demuth and Schaffner.[57] They predicted that this tricyclic ketone would provide "versatile building blocks for the total synthesis of polycyclopentanoids and related compounds".[58] Since then, many natural compounds have been synthesized using this ketone as a key intermediate,[58-60] including (-)-coriolin,[61] (-)-silphiperfol-6-en-5-one,[62] and (±)-modhephene.[63]

The preparation of tricyclo[3.3.0.0^{2,8}]octan-3-one **168** has been achieved by different routes, including metal carbene insertion reactions.[56,64]

The route via oxa-di-π-methane (ODPM) rearrangement of bicycle **171** is apparently expeditious, as shown in Scheme 2-13.[58] This rearrangement is easy to perform, by just simply irradiating the dilute solution of **171** in a triplet-sensitizing solvent, such as acetone or acetophenone. This photochemical rearrangement always gives very good yields. Racemic **171** could be readily enantiomerically separated by protecting the carbonyl with diethyl (R,R)-tartrate,



171 (R=H, R, OR, CO_2R) **168**

Scheme 2-13

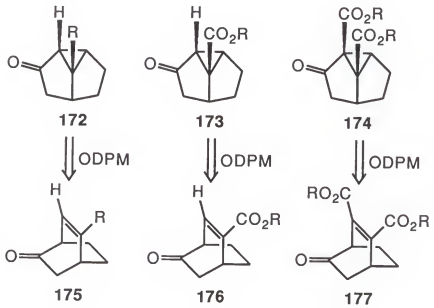
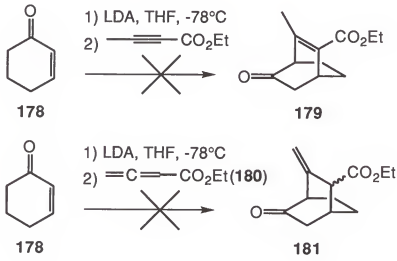


Figure 2-5
The tricyclo[3.3.0.$0^{2,8}$]octan-3-one substrates and their ODPM rearrangement precursors

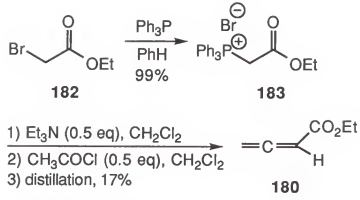
separating the ketal diastereomers by chromatography, and then deprotecting the carbonyl through acidic hydrolysis.[58,59] Each enantiomer can be thus obtained in >98% e.e. (enantiomeric excess). This offers a synthetic approach for enantiomerically pure cyclopentanoid natural products.

To study the O-stannyl ketyl-promoted cyclopropane fragmentation in tricyclo[3.3.0.0^{2,8}]octan-3-one substrates, three substrates (**172**, **173** and **174**) were planned, as shown in Figure 2-5. Using these compounds, the significance of radical-stability effects relative to stereoelectronic effects in the fragmentations could be examined. So could the influence of the C1- and C2-substituents to the reactions.



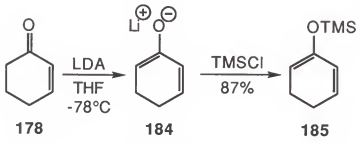
Scheme 2-14

To synthesize the analogs of **176**, well-documented double Michael addition was initially used.[65] Unfortunately, the starting molecules extensively polymerized (Scheme 2-14). Ethyl allenecarboxylate **180** was prepared according to Lang's procedure, as shown in Scheme 2-15.[66] Its low yield was due to the difficulty in removal of a large amount of solid Ph_3PO byproduct before distillation. These double Michael approaches were abandoned.



Scheme 2-15

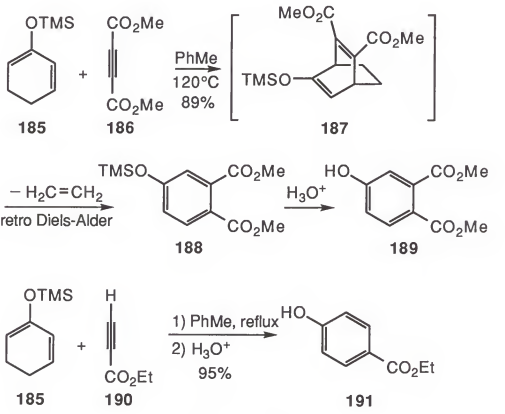
Diels-Alder cycloaddition was chosen to synthesize **176** and **177**, using trimethylsilyloxycyclodiene **185** and mono- or double-ester-activated acetylene as dienenophile.[67] Diene **185** was prepared in 87% yield from cyclohexenone **178** by Rubottom's method, as shown in Scheme 2-16.[68]



Scheme 2-16

The Diels-Alder reaction of **185** and dimethyl acetylenedicarboxylate (DMAD) **186** was carried out in refluxing toluene at 120°C. However, instead of bicyclic adduct **177**, phenol **189** was obtained in 89% yield, as shown in Scheme 2-17. The formation of this phenol was rationalized with a retro Diels-Alder process occurring at the relatively high reaction temperature, through which ethylene was liberated. Aromaticity was the obvious driving force.

Similarly, the reaction of **185** with ethyl propiolate **190** in refluxing toluene produced phenol **191** in 95% yield, instead of desired bicycle **176**.

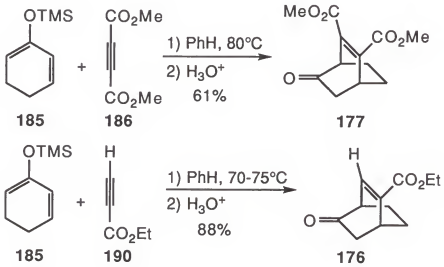


Scheme 2-17

In order to prevent the retro Diels-Alder process, the reaction of **185** and DMAD **186** was performed at a lower temperature (80°C in benzene). The Diels-Alder reaction worked very well, giving desired cycloadduct **177** in 61% yield, as shown in Scheme 2-18. Phenol **189** was still produced, but only as a minor product this time.

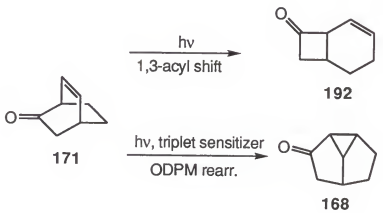
The reaction of **185** and **190** was carried out in refluxing benzene for 2 days. Adduct **176** was isolated in 35% yield, with retro-[4+2] product **191** as the major product. This cycloaddition then was performed in a sealed flask at 70-

75°C. After 7 days, **176** was afforded in 88% yield, with a small amount of phenol **191**.



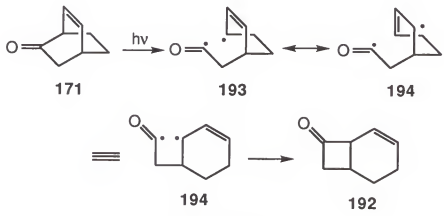
Scheme 2-18

To improve the yields, these Diels-Alder reactions were attempted at still lower temperatures (0°C-60°C). Disappointingly, the reactions were too slow to be useful and the retro-[4+2] process still could not be completely suppressed. An effort to catalyze the cycloaddition with Lewis acid $SnCl_4$ at -78°C was also unsuccessful.



Scheme 2-19

With precursors **176** and **177** in hand, it was time to examine the ODPM rearrangement.[69] This bicyclo[2.2.2]octenone photorearrangement was first investigated by Givens in 1971.[70] As shown in Scheme 2-19, direct photochemical irradiation of bicyclo[2.2.2]octenone **171** afforded 1,3-acyl shift product **192**, while triplet-sensitized irradiation gave ODPM rearrangement product **168**.[58,59]



Scheme 2-20

The mechanism of these photochemical rearrangements have been well-studied.[58] The 1,3-acyl migration is initiated by photolytic α-cleavage of the ketone to acyl-allyl diradical, which has the option of either regenerating the starting material or recombining in the alternative allylic position and forming 1,3-shift product **192**, as shown in Scheme 2-20. This reaction occurs from the n,π^* singlet excited state $S_1(n,\pi^*)$ and also from the triplet excited state $T_2(n,\pi^*)$, as indicated in Figure 2-6.

ODPM rearrangement occurs from the lowest lying excited triplet state $T_1(\pi,\pi^*)$.[58] E_T^{sens} represents the excited-state energy of the selected triplet sensitizer. After the triplet sensitizer reaches its excited state by absorbing the

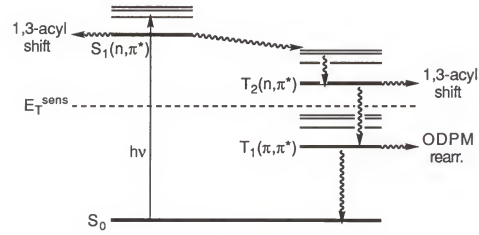
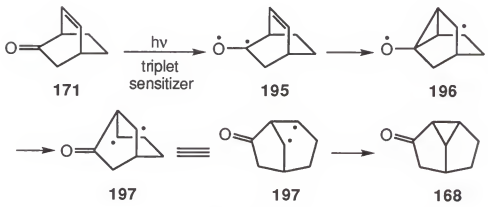


Figure 2-6
Energy diagram of bicyclo[2.2.2]octenone **171**



Scheme 2-21

irradiation energy hv, the sensitizer delivers and unloads energy E_T^{sens} to bicyclo[2.2.2]octenone **171**. If the energies of T_1, T_2 and E_T^{sens} have been carefully adjusted by choosing the right triplet sensitizer and optimizing the irradiation wavelength and enone concentration, the E_T^{sens} can be set exactly between T_2 and T_1. In this case, energy E_T^{sens} is exclusively transferred from the sensitizer to bicyclo[2.2.2]octenone's T_1 to secure ODPM rearrangement to occur.[58] T_1-excited enone **171** can be expressed by diradical **195**, as shown in Scheme 2-21. The carbon-centered radical adds onto the alkene to form

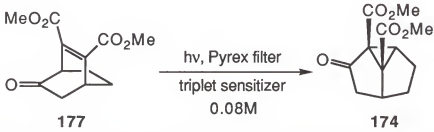
cyclopropane-separated diradical **196**. The oxygen-centered radical cleaves the cyclopropane to give **197**, where coupling of the two carbon-centered radicals yields tricyclic ketone **168**. This photochemical sequence is termed "oxa-di-π-methane" or "ODPM" rearrangement.[58]

The two best reaction conditions for an efficient ODPM rearrangement have been reported to be: 1) acetone as the sensitizer and solvent, enone concentration less than 2%, λ_{irr} =300nm; 2) acetophenone as the sensitizer, pure acetophenone or 20% acetophenone in acetone, benzene or cyclohexene as the solvent, enone concentration less than 10%, λ_{irr} >340nm.[59] The advantage in acetone serving as sensitizer is the ease in workup and isolation of the product, due to the low boiling point (56°C) of acetone. However, the enone concentration should not exceed 2% in acetone; otherwise the direct energy absorbance of the enone will become noticeably competitive, giving 1,3-acyl shift byproduct **192**. When acetophenone serves as sensitizer at >340nm, the direct enone absorbance is negligible, and the enone concentration can be as high as 10%. The negative side of acetophenone is the difficult removal of this compound (boiling point 202°C), after the rearrangement is complete.

A 450W Hanovia medium-pressure mercury-vapor lamp was used to irradiate the ODPM rearrangement precursors. In order to match the literature wavelength mentioned above, the irradiation was conditioned with a Pyrex glass filter. Pyrex glass is capable of absorbing most of the <320nm irradiation.

To compare the efficiency of acetone and acetophenone as sensitizer, ODPM rearrangement was performed using a 0.08M solution of **177**, as shown in Scheme 2-22. When acetone was used, the photorearrangement was complete in 24 hours, smoothly affording **174** in 83% yield. When acetophenone was the solvent and sensitizer, the reaction finished in 12 hours. After most acetophenone was distilled away, the residue was chromatographed

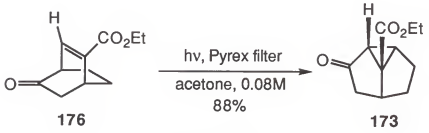
to separate the remaining acetophenone and rearrangement product. Tricyclic **174** was isolated in 92% yield. Obviously, acetophenone was a more efficient sensitizer for ODPM rearrangement, giving higher yield in shorter irradiation time. However, due to the tedious acetophenone separation, acetone was preferred as our triplet sensitizer.



177 **174**

sensitizer & solvent	irradiation time	isolated yield
acetone	24 hrs	83%
acetophenone	12 hrs	92%

Scheme 2-22



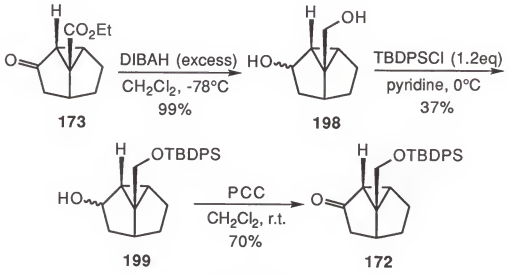
176 **173**

Scheme 2-23

The ODPM rearrangement of **176** was accomplished in 84% yield after 24-hour irradiation in acetone, giving tricyclic substrate **173**. The yield was improved to 88% when **176** was irradiated for 48 hours, as shown in Scheme 2-23.

The preparation of C1-alkyl-substituted substrate **172** (Figure 2-5) started directly from **173**, as shown in Scheme 2-24. Tricycle **173** was reduced

using excess amount of diisobutylaluminum hydride (DIBAH, 5 equivalents) to diol **198** in 99% yield. The primary hydroxy group was selectively protected with 1.2 equivalent of t-butyldiphenylsilyl chloride (TBDPSCl). Oxidation of secondary alcohol **199** to ketone **172** was done with PCC in 70% yield. Bearing t-butyldiphenylsiloxymethyl at its C1 position, compound **172** was suitable for studying the influence of C1-alkyl on the O-stannyl ketyl-promoted tricyclo[3.3.0.0^{2,8}]octan-3-one fragmentation. Thus, substrates **170**, **171** and **172** planned in Figure 2-5 were all synthesized.



Scheme 2-24

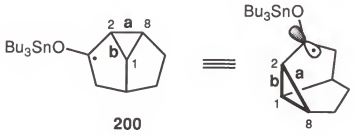
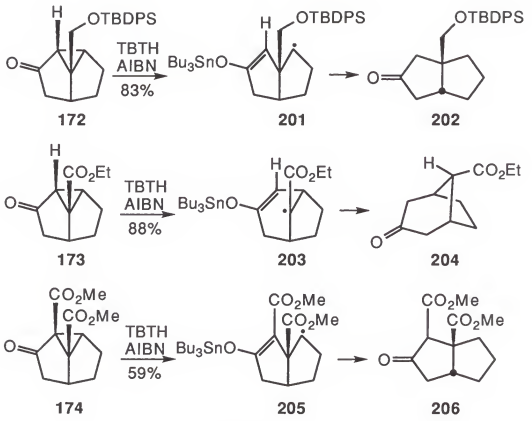


Figure 2-7
O-stannyl ketyl of tricyclo[3.3.0.0^{2,8}]octan-3-one

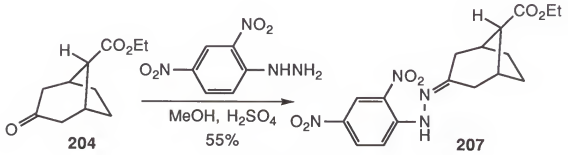
For tricyclo[3.3.0.0^{2,8}]octan-3-one substrates, once O-stannyl ketyl **200** forms, bond **a** (C2-C8) has better overlap with the ketyl's sp^2-like orbital than bond **b** (C1-C2) does, as shown in Figure 2-7. Thus, stereoelectronic effects favor bond **a** cleavage in the fragmentation.[35]

The reactions of tricyclic substrates **172**, **173** and **174** with TBTH and AIBN in refluxing benzene are shown in Scheme 2-25.[35] Tricyclic **172** (R_{C1}=alkyl) afforded bond **a** cleavage product **202** in 83% yield in 4 hours. Ester **173** (R_{C1}=ester) gave a single diastereomer **204** in 88% yield in 1 hour. When the reaction time was extended to 5 hours, the yield was improved to 94%. Interestingly, diester substrate **174** (R_{C1}=R_{C2}=ester) produced only bond **a** cleavage product **206** in 59% yield, though its C1-ester function was capable of stabilizing the radical formed by bond **b** cleavage. It was contradictory that **174**'s C1-ester did not play a role in the cyclopropane fragmentation, while **173**'s C1-ester apparently overwhelmed stereoelectronic effects.[35] Substrates **173** and **174** differed only by the presence of an additional ester group at the C2 position of **174**.

Unequivocal confirmation of the product structures shown in Scheme 2-25 was required. Structure **204** had C_2 symmetry, possessing 3 pairs of identical carbon atoms. Its ^{13}C NMR (nuclear magnetic resonance) spectrum clearly supported this C_2 symmetrical structure. Only 8 carbon peaks were recorded in the spectrum. Obviously, the 3 pairs of carbon atoms only gave 3 single peaks due to the identical chemical shift of the two individual carbon atoms in each pair. To desymmetrize **204** and observe all the carbon peaks, it was converted to 2,4-dinitrophenylhydrazone derivative **207,** as shown in Scheme 2-26. Now there were three additional carbon peaks appearing in the NMR spectrum. Thus, the symmetrical structure of **204** was confirmed.

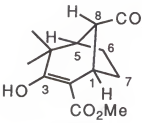


Scheme 2-25



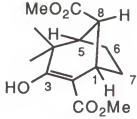
Scheme 2-26

The structural assignment of **204** was determined on the basis of proton NMR analysis and comparison with the spectra of known structurally-similar compounds **208L** and **208R** reported by Yates and Stevens.[71] The two possible structures of **204** are given in Figure 2-8: **204L** and **204R**. Inspection of a molecular model of **204L** showed that the dihedral angle between C1-H or



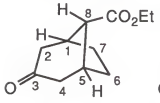
208L

C8-H: δ 2.86, singlet



208R

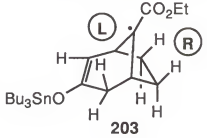
C8-H: δ 2.67, triplet, J=4Hz



204L

C8-H: δ 2.77, singlet

204R



203

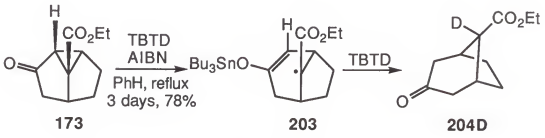
Figure 2-8

The structural assignment of **204**

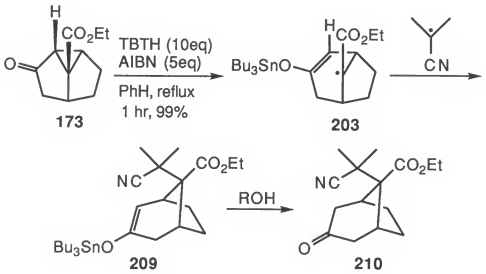
C5-H and C8-H bonds was about 90°, which would result in negligible coupling between the C8-H and the C1/C5-H.[71,72] A molecular model of **204R** showed that the corresponding dihedral angle was 45°, which would result in the splitting of the C8-H signal into a triplet with coupling constant J of about 4 Hz.[71,72] The observed **204**'s C8-H resonance was a singlet at 2.77 ppm. This signal was in nice agreement with that of structurally-similar **208L** (singlet at 2.86 ppm). This indicated that **204L** was the single diastereomer produced in the cyclopropane fragmentation of **173**.

Thus, excellent stereoselectivity in the hydrogen abstraction from TBTH was achieved for radical intermediate **203** (Figure 2-8). TBTH could approach the C8 radical site from the **L** face or the **R** face. Due to the presence of flat tin(IV) enolate, the **L** face was much more sterically open than the **R** face. Therefore, TBTH selectively approached from the **L** face to afford **204L**.

To confirm the presence of radical intermediate **203** in the cyclopropane fragmentation, the reaction of **173** and tributyltin deuteride (TBTD) was performed to trap out this intermediate by deuterium abstraction, as shown in Scheme 2-27. Symmetrical **204D** was isolated in 78% yield. Comparison of the ^{1}H and ^{13}C NMR spectra of **240D** and **240** indicated that the deuteration occurred at C8 position of **240D**. Key intermediate **203** was thus confirmed.



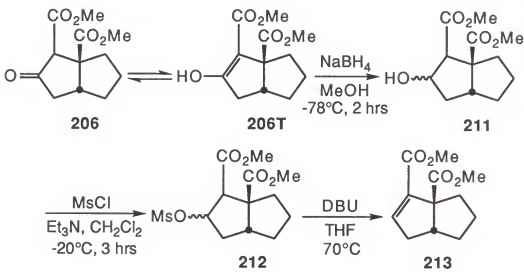
Scheme 2-27



Scheme 2-28

Surprisingly, when excess amount of AIBN was used in the reaction of **173** and TBTH, nitrile **210** was obtained in quantitative yield, as shown in Scheme 2-28. This nitrile arose from the coupling reaction of intermediate **203**

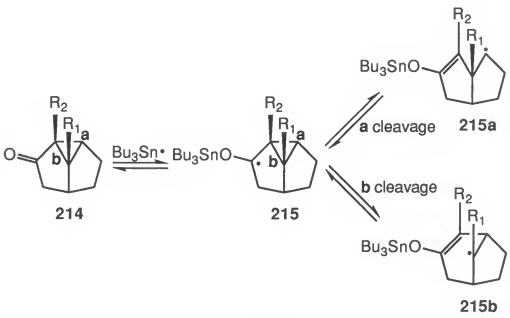
with cyanoisopropyl radical, formed in thermal decomposition of AIBN (Scheme 1-1). It was interesting that **203** coupled faster with cyanoisopropyl radical than abstracting a hydrogen from TBTH. The formation of **210** also confirmed presence of **203**. The participation of cyanoisopropyl radical in free radical reactions is known in literature.[14b]



Scheme 2-29

The structure of cyclopropane-opening product **206** needed to be confirmed. The spectroscopic evidence was not conclusive for this structure, because the diester ketone product was complicated by an equilibrium mixture with its tautomer **206T**. Both were clearly visible on the NMR time scale. To conclusively confirm the structure, the C3-carbonyl was removed using a three-step sequence illustrated in Scheme 2-29. The **206**/**206T** mixture was reduced to alcohol **211** with sodium borohydride at -78°C. The alcohol was activated using mesyl chloride at -20°C. Elimination of **212** with 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) in refluxing THF afforded **213** as the sole isolable product. The ^{13}C NMR and the attached proton test (APT) study for **213** revealed presence of 4 quaternary carbons (176.6, 164.6, 137.6, 65.7

ppm), 2 CH units (144.8, 49.4 ppm), 4 CH_2 units (39.7, 35.6, 35.4, 26.1 ppm) and 2 CH_3 units (52.2, 51.5 ppm) in this compound. These NMR data conclusively confirmed the assigned structure of **213**.[35]



Scheme 2-30

To explain the contrasting cyclopropane fragmentation results from very similar structures in Scheme 2-25, it was proposed that stereoelectronic effects initially favored the cleavage of bond **a** in all three precursors (**172**, **173** and **174**), and **215a** initially formed in each case, as shown in Scheme 2-30.[35] It was proposed that a reverse reclosure also involved, though cyclopropane scission occurred at a much higher rate to release ring strain. If R_2=H, as in **172** and **173**, the reclosure was more facile, because no substituent was present at C_2 to sterically hinder this center. At this point, cleavage of bond **b** was likely to occur if there was a sufficient driving force. For **173** (R_1=CO_2Et), the driving force of radical-stability effects was significant enough to cleave bond **b**, because its C1-ester could much stabilize radical **215b** (i.e. **203**). Once this

radical was stabilized, the reverse reclosure was energetically unfavorable and less likely. Radical **203** thus remained until hydrogen abstraction from TBTH occurred to give **204**.

Substrate **172** (R_1=$CH_2OTBDPS$) lacked radical-stabilizing substituent at its C1 position. Though the **a** cleavage was reversible, there was no driving force for the cyclopropane scission to proceed by the stereoelectronically-unfavored bond **b** cleavage pathway. Thus, radical **215a** (i.e. **201**) underwent hydrogen abstraction from TBTH, yielding **202** after hydrolysis.

Diester substrate **174** (R_1=R_2=CO_2Me) was different. After the stereoelectronically-favored bond **a** cleavage occurred initially, the R_2-ester group sterically blocked the reclosure of radical **215a** (i.e. **205**) to **215**. Similar rate-retarding effects by blocking 5-hexenyl radical cyclization at the internal C5 position of the alkene have been well-established.[1] But they are not yet well-understood for 3-butenyl radical cyclizations. It is further noteworthy that if R_2=CO_2Me, as in the case of **174**, the reclosure prevents conjugation of the ester with the olefin, which is also energetically less favorable. Thus, **205** was the cyclopropane fragmentation product, giving **206** after hydrogen abstraction from TBTH and hydrolysis.

In conclusion, the O-stannyl ketyl-promoted cyclopropane fragmentations were studied using various substrates: simple cyclopropanes, cyclopropanes fused on other rings, and tricyclo[3.3.0.$0^{2,8}$]octan-3-ones. These ketyl-mediated fragmentations are governed by both stereoelectronic effects and radical-stability effects. The significance of the latter effects depends on the substitution pattern of the cyclopropane. These studies enable us to apply the cyclopropane fragmentations to organic synthesis, which is the subject of next chapter.

CHAPTER 3
APPLICATIONS OF THE O-STANNYL KETYL-PROMOTED CYCLOPROPANE FRAGMENTATIONS TO THE SYNTHESIS OF TRIQUINANE COMPOUNDS

New methods for the construction of condensed cyclopentanoid ring systems (polyquinanes) continue to be developed at an accelerated pace since the 1970s.[60] Among important naturally occurring polyquinanes are tricyclic polyquinane sesquiterpenes, which are termed "triquinanes" and can be classified as linear, angular or propellane according to ring fusion (Figure 3-1).[73a] Triquinanes come from a wide variety of natural sources and many possess significant antibiotic and/or antitumor activity.[73a] These structurally interesting triquinane natural products provide a particular vehicle for the application of various new cyclopentanoid synthetic methodologies.[60]

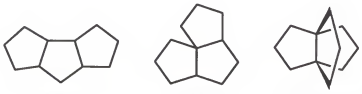


Figure 3-1
The skeletons of triquinane compounds

There are more than 40 different triquinane terpenes found in the nature.[74] Figure 3-2 shows the structures of several natural triquinanes. Among them, linear triquinane capnellene (**216**), hirsutic acid (**217**) and coriolin (**218**) have three cyclopentane rings linearly *cis,anti,cis* fused in a straight chain.

Angular triquinane subergorgic acid (**219**) and isocomene (**220**) possess three cyclopentane rings *cis,anti,cis* fused in an angled array. Modhephene (**221**) is a propellane triquinane.

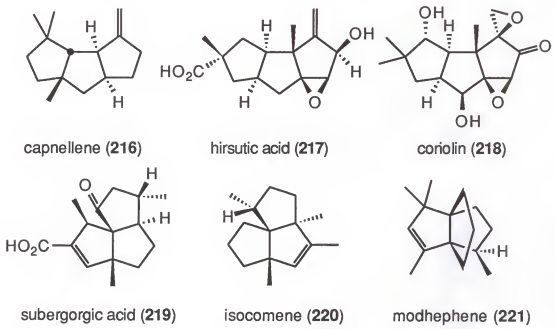
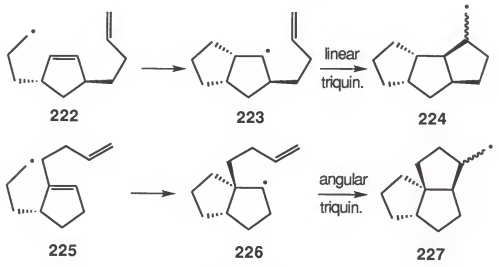


Figure 3-2
Several natural triquinane compounds

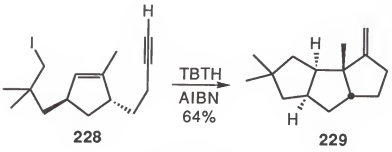
The field of triquinane synthesis has greatly expanded since hirsutic acid **216** was first synthesized in 1974 by Matsumoto.[75] Numerous synthetic routes were attempted, and every major naturally occurring triquinane has been successfully prepared in organic labs.[60,74] Many triquinanes have even several syntheses using a variety of approaches, such as the compounds listed in Figure 3-2.

Among the powerful approaches for triquinane synthesis is a free radical tandem cyclization sequence to construct two new cyclopentanes fused on the parent cyclopentanoid substrate in a single transformation. This synthetic route was elaborated by Curran and coworkers.[73] In this route, a bromide or iodide

must be properly placed in the cyclization precursor. With treatment of TBTH and AIBN, this bromide or iodide produces a reactive free radical (**222** and **225**), which cyclizes onto a cyclopentene to form a bicyclic diquinane radical (**223** and **226**), as shown in Scheme 3-1.[73e] This new radical then cyclizes onto a tethered olefin or alkyne to produce a linear (**224**) or angular (**227**) triquinane skeleton. One such example is Curran's synthesis of hirsutene **229**, as shown in Scheme 3-2.[73a,b] For this linear triquinane synthesis, the *trans* stereochemistry of the two tethers in radical reaction precursor **228** is essential for accomplishment of the naturally-occurring *cis,anti,cis* ring fusion in the tandem cyclization sequence.



Scheme 3-1

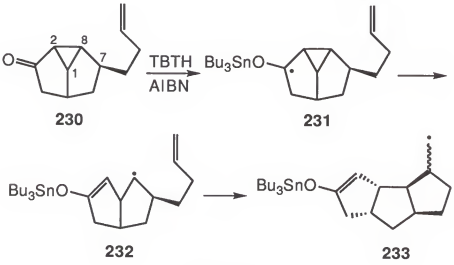


Scheme 3-2

One main drawback of Curran's approach is that too many steps are usually required to prepare the tandem cyclization precursor. For example, a 12-step synthesis was used to synthesize precursor **228** in Curran's route for hirsutene **229**.[73a,b] All these steps were directed to setup the combination of a multiple-bond tether and a diquinane radical (**223** or **226**).

Chapter 2 has reported our studies on the O-stannyl ketyl-promoted cyclopropane fragmentations. The fragmentation of tricyclo[3.3.0.0^{2,8}]octan-3-one substrates selectively gives the bond **a** (C2-C8) cleavage product, unless a radical-stabilizing substituent is at the C1 position. As shown in Scheme 2-25, the cyclopropane fragmentations of **172** and **174** produced diquinane radicals **201** and **205**, which could be utilized to achieve triquinane synthesis.

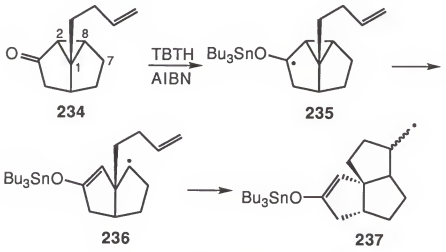
To thus accomplish triquinane synthesis on the basis of our previous studies, a novel O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequence was envisioned. As illustrated in Scheme 3-3, if



Scheme 3-3

an olefin or alkyne tether was placed at C7 (**230**), after the cyclopropane fragmentation, the cyclization of diquinane radical **232** would yield linear

triquinane **233**. If the tether was placed at C1 (**234**), the radical cyclization would produce angular triquinane skeleton **237** (Scheme 3-4). This work would generate a new general approach towards the synthesis of triquinane compounds by taking advantage of tricyclo[3.3.0.0^{2,8}]octan-3-ones. Compared to Curran's general route, this approach could reach the final triquinane cyclization stage in a shorter and more efficient manner. Much of this simplicity could be found in the use of a ketone (**230** or **234**) to initiate the radical process, rather than a halide.



Scheme 3-4

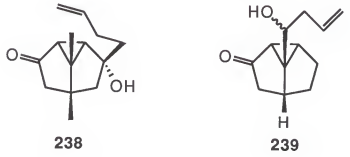
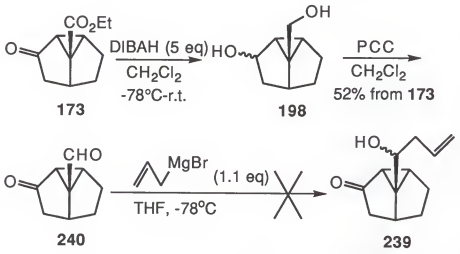


Figure 3-3
The model precursors for cyclopropane fragmentation-cyclization sequence and triquinane skeleton synthesis

To examine this O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequence and demonstrate this new triquinane synthesis approach shown in Schemes 3-3 and 3-4, two model precursors **238** and **239** were planned, as exhibited in Figure 3-3.[36,37] Note that they differ primarily by placement of the olefin tether.

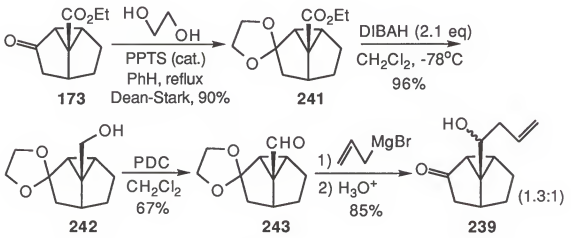
To synthesize precursor **239** from 1-ethoxycarbonyltricyclo[3.3.0.$0^{2,8}$]-octan-3-one **173**, which had been prepared in chapter 2, the route shown in Scheme 3-5 was initially planned. Tricycle **173** was reduced to diol **198** with excess DIBAH. Oxidization to dicarbonyl **240** with PCC was achieved in 52% yield for these two steps. To finish the preparation of **239**, it was attempted to take advantage of the reactivity difference between a ketone and a presumably



Scheme 3-5

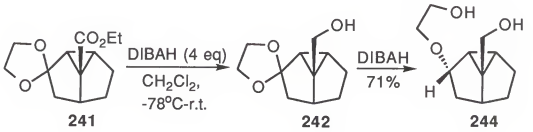
more reactive aldehyde by treatment with 1 equivalent of allyl Grignard reagent. Disappointingly, the reactivity difference between the ketone and aldehyde carbonyls in **240** was negligible and the selectivity in this addition was very poor. Even when 1.1 equivalent of allylmagnesium bromide was added dropwise to a very dilute **240** solution (0.1 M) at -78°C, double-Grignard-

addition product was still obtained along with remaining unreacted **240**. In order to add an allyl unit to the aldehyde, the ketone had to be protected before the Grignard reaction. Thus, our synthetic approach was modified to that shown in Scheme 3-6.[36]



Scheme 3-6

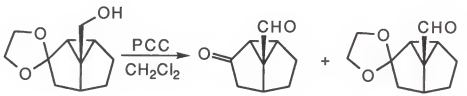
Protection of the ketone carbonyl of **173** using ethylene glycol and mild catalyst PPTS (pyridinium p-toluenesulfonate) gave ketal **241**, as shown in Scheme 3-6. A Dean-Stark tube was attached to the reaction flask. This protection was complete in 12 hours in 90% yield. To reduce the C1-ester group



Scheme 3-7

of **241**, 4 equivalents of DIBAH were used in the first attempt. Interestingly, the ketal protective group was reductively cleaved by the excess amount of DIBAH remaining after the ester reduction had been complete, and diol **244** was isolated in 71% yield (Scheme 3-7). Similar reductive cleavages of ketals and acetals by hydride donors are known in literature.[76]

In next attempt, only 2.1 equivalents of DIBAH were added to **241** at -78°C, as shown in Scheme 3-6. Primary alcohol **242** was yielded in 96% yield, and no overreduced product **244** was found. To oxidize **242** to **243**, PCC was initially used. However, during the oxidation, the ketal protection group was cleaved. Dicarbonyl **240** was obtained as the major product in 67% yield, while **243** was isolated in a yield less than 5% (Scheme 3-8). This carbonyl deprotection was rationalized by the acidity of the PCC reagent.

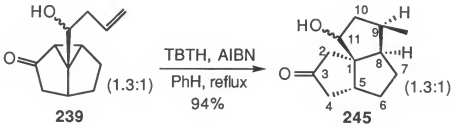


242 **240** (67%) **243** (<5%)

Scheme 3-8

To avoid the deprotection, a slightly basic oxidant pyridinium dichromate (PDC) was used, oxidizing **242** smoothly to desired ketal aldehyde **243** in 67% yield, as shown in Scheme 3-6. The allyl tether was added to the aldehyde through a Grignard reaction. The ketal protective group was removed during the normal Grignard acidic workup, giving precursor **239** in 85% yield. The GC ratio of the two **239** diastereomers was 1.3 to 1. These two diastereomers were not separable from each other by column chromatography.

Now it was time to examine the proposed O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization sequence and angular triquinane synthesis approach (Scheme 3-4). Refluxing **239** in benzene at a concentration of 0.1 M for 14 hours, with 2 equivalents of TBTH and 1 equivalent of AIBN, smoothly furnished angular triquinane **245** in 94% yield, as shown in Scheme 3-9. The GC ratio of the major cyclization products (the C11-diastereomers) and the minor cyclization products was 57:1. The GC ratio of the **245** C11-diastereomers was still 1.3:1.[36]

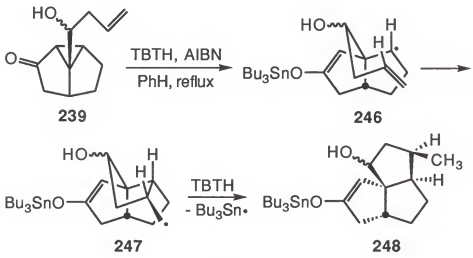


239 **245**

Scheme 3-9

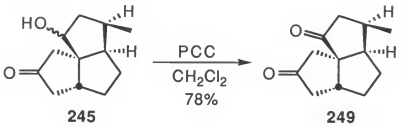
NMR was used to establish the stereochemistry of triquinane **245** at the C9 center. Based on Whitesell's ^{13}C NMR studies,[77] if the C9-methyl was endo, the C9 resonance should be around 15 ppm and the C8 resonance should be around 33.0 ppm (for endo C11-OH) and 35.4 ppm (for exo C11-OH). If the C9-methyl was exo, the C9 resonance should be around 19 ppm and the C8 resonance should be around 37.4 ppm (for endo C11-OH) and 39.8 ppm (for exo C11-OH). The ^{13}C NMR spectrum of **245** clearly indicated that for the major cyclization products, the C9-methyls were at 14.5 and 14.6 ppm, and the C8-tertiary centers appeared at 31.0 and 33.2 ppm. These characteristic ^{13}C NMR peaks were in excellent agreement with those calculated for the endo-C9-methyl stereomers by Whitesell's method. Thus, the C9-methyl stereochemistry of the major products **245** was established as endo.

Excellent stereochemical control was realized in the O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization sequence shown in Scheme 3-9, where the C9-methyl endo:exo stereoselectivity was 57:1 in the 5-exo-trig radical cyclization. Beckwith's chair-like transition state **246-247** explains the endo-C9-methyl stereochemistry in **245**, as shown in Scheme 3-10.[16,17,36]



Scheme 3-10

In order to finally obtain a single triquinane diastereomer and simplify characterization, PCC oxidation was performed to remove the C11 sp^3 stereocenter of **245**. The oxidation was complete in 1 hour, producing angular triquinane diketone **249** in 78% yield, as shown in Scheme 3-11. In the ^{13}C NMR of **249**, the C9-methyl was at 16.2 ppm and the C8 at 30.1 ppm. According to Whitesell's studies,[77] if the C9-methyl was endo, it should appear at about 15 ppm and the C8 at 30.1 ppm; if the C9-methyl was exo, it should be around 19 ppm and the C8 at about 34.5 ppm. The ^{13}C NMR resonance for **249** was in excellent agreement with that calculated for the endo-C9-methyl stereoisomer. The endo stereochemistry of the C9-methyls in **245** and **249** was reconfirmed.

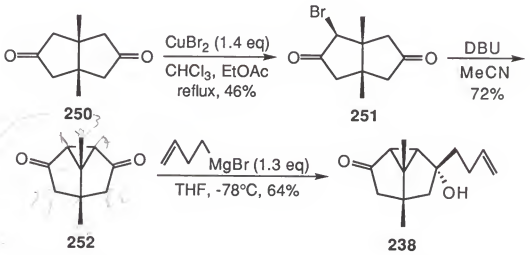


245 **249**

Scheme 3-11

This study examined the O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequence and a novel approach for angular triquinane synthesis. Excellent stereoselectivity was accomplished. It is worth noting the efficiency of this new method. The entire synthetic sequence is very efficient, producing triquinane **245** in 5 steps in 46% overall yield from **173**, which can be prepared in 3 steps in 67% overall yield from 2-cyclohexen-1-one **178**.

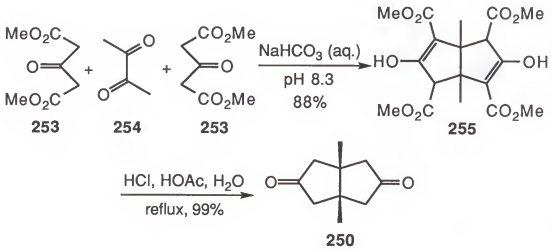
To synthesize precursor **238**, which could lead to construction of a model linear triquinane and another example of O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization sequence, the approach shown in Scheme 3-12 was planned.[37]



250 **251** **252** **238**

Scheme 3-12

Starting material *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione **250** was prepared using Weiss condensation,[78] as shown in Scheme 3-13. The 2:1 condensation of dimethyl 1,3-acetonedicarboxylate **253** and 2,3-butanedione **254** was carried out in an aqueous buffer solution of sodium bicarbonate (pH 8.3). Condensation product **255** gradually formed and separated from the solution as white solid in 88% yield. The mechanism of this 2:1 condensation has been discussed by Cook.[79] Hydrolysis of **255** in a refluxing aqueous mixture of HCl and HOAc yielded bicyclic dione **250** in 99% yield.

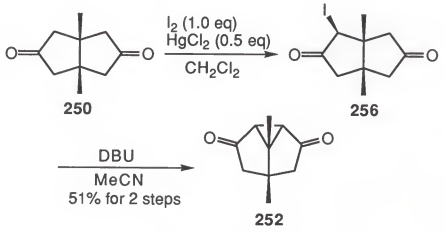


Scheme 3-13

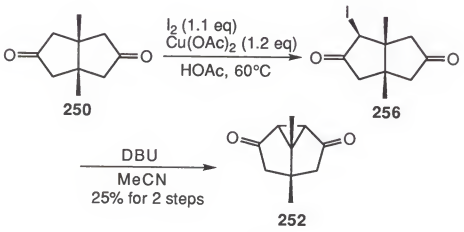
To prepare tricyclic dione **252**, Gleiter's method was first used, as shown in Scheme 3-12.[80] Diketone **250** was monobrominated by adding 1.4 equivalent of $CuBr_2$ to the refluxing reaction mixture. Copper(II) bromide had to be added very slowly in a very little amount each time, otherwise multiple-bromination products would predominate. Monobromide **251** was produced in 46% yield. Because of the cup-like shape of molecule **250**, bromide approached primarily from the exo face, and so the bromide stereochemistry in **251** was exo. Treatment of **251** with 1.1 equivalent of DBU smoothly furnished

symmetrical tricyclic dione **252** in 72% yield.[80] In this reaction, only the deprotonation at one position could result in dehydrobromination, constructing the fused cyclopropane unit in dione **252**.

In order to improve the yield of **252**, iodination of **250** was attempted. Barluenga's methodology was used to prepare iodide **256**, as shown in Scheme 3-14.[81] Iodide **256** was not characterized and purified. Crude iodide **256** was directly used to produce **252** in 51% yield for these two steps. Thus, the yield for **252** from **250** was increased from 33% ($CuBr_2$ method) to 51%.



Scheme 3-14



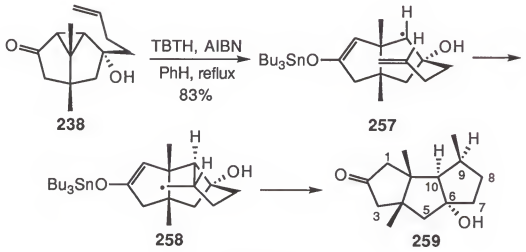
Scheme 3-15

Horiuchi's iodination methodology was also attempted, as shown in Scheme 3-15.[82] However, this iodination method was so messy that several unknown side products also formed. Solvent acetic acid was difficult to remove. The two-step yield from **250** to **252** was only 25%, much lower than that by Barluenga's iodination method (Scheme 3-14).

The preparation of precursor **238** was straightforward from tricyclic ketone **252**, as shown in Scheme 3-12. Addition of 1.3 equivalent of 3-butenylmagnesium bromide to **252** at -78°C afforded **238** in 64% yield. Because of its cup-like molecule shape, the incoming Grignard reagent could approach **252**'s carbonyls only from the exo face. This exo:endo face selectivity was >100:1 by GC. This stereoselective addition of the Grignard reagent to the most accessible exo face was important for later elaboration to the *cis,anti,cis*-configuration of the model linear triquinane skeleton. Due to the C_2 symmetry of **252**, same addition product was obtained no matter which carbonyl group reacted.

O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequence using precursor **238** was examined, as shown in Scheme 3-16.[37] Refluxing **238** in benzene at a concentration of 0.25 M overnight, with 3 equivalents of TBTH and 1 equivalent of AIBN, gave linear triquinane **259** in 83% yield. The exo stereochemistry of the olefin tether in **238** secured the requisite *cis,anti,cis*-configuration in **259**, which occurs in all natural linear triquinane compounds. The newly formed C9-methyl (13.7 ppm in ^{13}C NMR) was established as endo for the major product, by comparison with ^{13}C NMR studies of closely related fused-cyclopentanes.[77] If the C9-methyl was endo, its resonance should be around 15 ppm. If it was exo, its resonance should be at about 20 ppm.[77] This C9-methyl endo:exo stereoselectivity in the 5-exo-trig radical cyclization was 4:1 by GC. This endo-C9-methyl stereoselectivity can be

explained using Beckwith's chair-like transition state **257**-**258**, as shown in Scheme 3-16.[16,17,37]



Scheme 3-16

In conclusion, it is demonstrated that the O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequences work very well. These sequences are highly stereoselective and the stereochemistry of their products can be predicted with accuracy. The yields of these sequences are excellent, considering the complexity of their products. Through these two examples, a novel and efficient synthetic approach toward angular and linear triquinane compounds is demonstrated. The work in this chapter marked the first real synthetic application of the O-stannyl ketyl-promoted cyclopropane fragmentations and enhances our understanding and knowledge of O-stannyl ketyl radicals.

CHAPTER 4
OTHER INVESTIGATIONS OF THE O-STANNYL KETYL-PROMOTED CYCLOPROPANE FRAGMENTATIONS

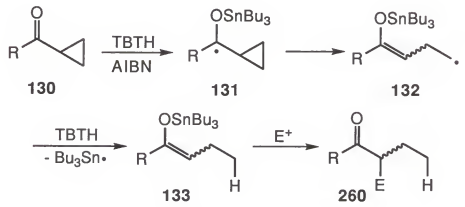
O-stannyl ketyl-promoted cyclopropane fragmentations were studied using a variety of substrates in previous chapters. In all the cases, after fragmentations, the radical centers were reduced by hydrogen abstraction from TBTH, and the tin(IV) enolates were hydrolyzed, though these radicals and enolates were synthetically useful. This chapter reports our preliminary results of application of the post-fragmentation tin(IV) enolates and trapping the post-fragmentation radicals with allyltributyltin.

Application of the Post-Fragmentation Tin(IV) Enolates

Tin(IV) enolates are useful intermediates and have been applied to many synthetic transformations.[6g,83] Recently Enholm demonstrated that tin(IV) enolates can be smoothly generated by the reaction of TBTH and α,β-unsaturated ketones,[34] as illustrated in Scheme 1-23. These tin(IV) enolates function very well in aldol and alkylation reactions.

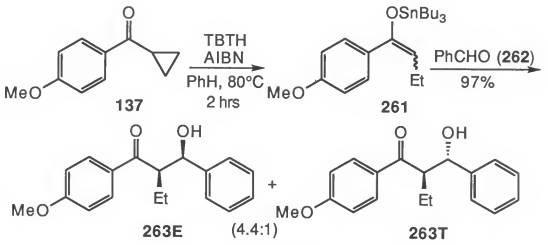
It has been well known since early 1970s that O-stannyl ketyl-promoted cyclopropane fragmentations readily generate tin(IV) enolates **133**,[25-27] as shown in Scheme 4-1. However, prior to the work described in this chapter, no synthetic exploration of this post-cyclopropane-fragmentation tin(IV) enolates had been reported. We envisioned that these tin(IV) enolates could be

synthetically useful by reacting with an electrophile, such as an aldehyde, ketone or alkyl halide, forming a new carbon-carbon bond.



Scheme 4-1

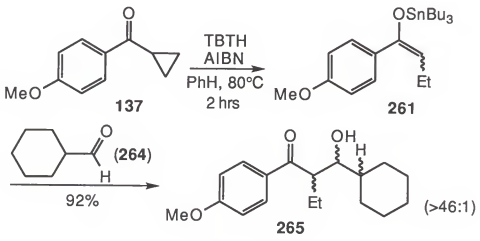
To examine synthetic application of these tin(IV) enolates, an aldol reaction was performed using cyclopropyl ketone **137**. The cyclopropane fragmentation finished in 2 hours, monitored by TLC. At room temperature, benzaldehyde **262** was added to tin(IV) enolate **261** and the reaction mixture



Scheme 4-2

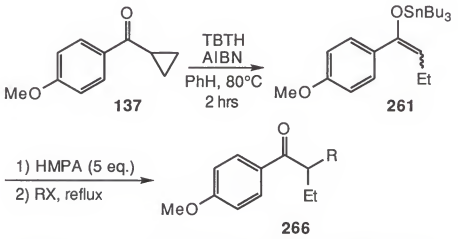
was stirred overnight, giving **263E/263T** in 97% yield as a mixture of erythro and threo diastereomers (4.4:1 by proton NMR integration), as shown in Scheme 4-2. The stereochemical assignment (erythro or threo) was made by ^{1}H NMR, using the well-accepted $J_{threo} > J_{erythro}$ relationship.[84] For the major product, the coupling constant between the carbinol proton and the methine proton was 4.5Hz; for the minor product, the coupling constant was 6.9Hz. Thus, the major product was assigned as erythro (**263E**). This assignment was confirmed by ^{13}C NMR spectra. According to Heathcock's studies,[85] the carbinol resonance of erythro β-hydroxycarbonyl compounds should be at 71.6-78.1 ppm and that of threo isomer should be higher at 74.0-82.5 ppm. The carbinol of the major product appeared at 73.8 ppm, while the carbinol of the minor product was at 75.6 ppm. The erythro assignment for the major product was thus confirmed. This is the first known O-stannyl ketyl-promoted cyclopropane fragmentation-aldol reaction.

A similar aldol reaction of tin(IV) enolate **261** and cyclohexanecarboxaldehyde **264** gave **265** in 92% yield, as shown in Scheme 4-3. A single diastereomer was isolated in excellent selectivity (>46:1 by GC).



Scheme 4-3

Alkylation reactions were also performed using tin(IV) enolate **261**, as shown in Scheme 4-4. When the cyclopropane fragmentation finished in 2 hours, 5 equivalents of HMPA were added at room temperature to increase the nucleophilicity of the enolate.[34c,d] Alkyl halide was next added and the mixture was refluxed overnight, giving alkylation product **267** (86%) and **268** (95%) in excellent yields. These are the first O-stannyl ketyl-promoted cyclopropane fragmentation-alkylation reactions.



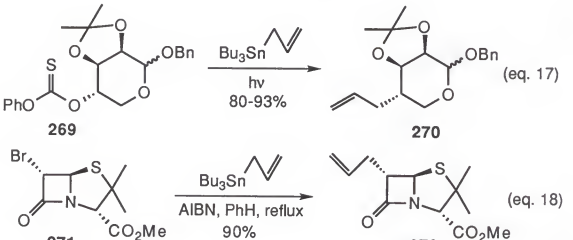
RX	alkylation product	isolated yield
	**267**	86%
	**268**	95%

Scheme 4-4

In a summary, tin(IV) enolates generated in the reactions of cyclopropyl ketones and TBTH are synthetically useful and work well in aldol and alkylation reactions. This exploration adds new depth to the O-stannyl ketyl-promoted cyclopropane fragmentations.

Cyclopropane Fragmentation-Allylation by Allyltributyltin

Chapter 1 has introduced Keck's allylation reactions (Schemes 1-8 and 1-9).[14] Historically, this allylation method dates back to 1973 when Migita and Pereyre first reported the free radical chain reaction of allylstannanes and organic halides.[86] In these reactions, a free radical was trapped by an allyl group, and a new carbon-carbon bond formed between the radical site and the allyl unit, as shown in Scheme 1-8. The first systematic investigation of this reaction was published in 1975.[87] In 1982, Keck demonstrated that this allylation reaction worked well in complicated substrates, tolerating the presence of acetals, ketals, ethers, epoxides, lactones, free hydroxyl groups, esters and sulfonate esters.[14a] Besides organic halides, Keck realized the allylation reactions of thioethers, thiocarbonyl esters and selenides. Keck found methallyltributyltin also suitable for this type of reaction.[14b]

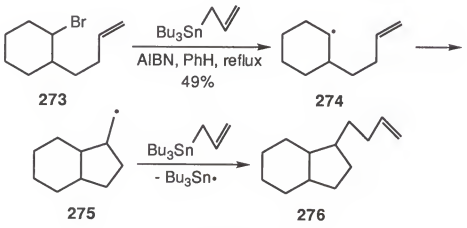


Scheme 4-5

Since then, this allylation method has steadily found further investigations and synthetic applications.[88] For example, Keck applied it to the

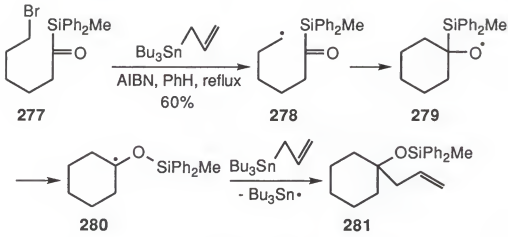
synthesis of pseudemonic acid C, as shown in eq. 17 in Scheme 4-5.[88e] Hanessian utilized this allylation method to prepare 6-α-allyl penicillanates **272**, as shown in eq. 18.[88f]

In 1985 Moriya applied allyltributyltin to radical cyclizations.[89] A typical free radical cyclization uses TBTH. The last step of this cyclization is reductive hydrogen abstraction by cyclized carbon-centered radical from TBTH. When allyltributyltin is used for cyclization, the hydrogen abstraction step is modified to a new carbon-carbon bond formation, without sacrificing the free radical chain process, as shown in Scheme 4-6. The chain process is maintained by regenerating tributyltin radical through an S_H2' reaction between cyclized radical **275** and allyltributyltin. Overall, an alkene-tethered ring **276** is produced in this reaction.



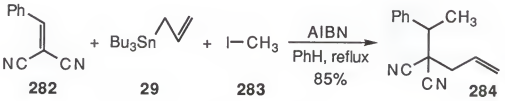
Scheme 4-6

A similar cyclization was examined by Curran, as shown in Scheme 4-7.[90] Curran used acylsilane as a radical acceptor. After the 6-exo cyclization, radical **279** rearranged to **280** which finally reacted with allyltributyltin to produce **281** in 60% yield.



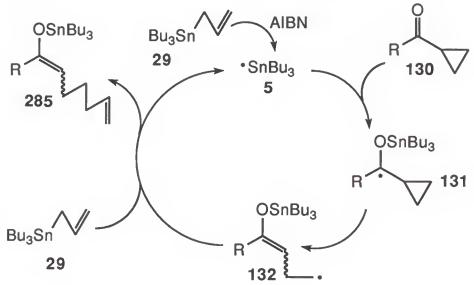
Scheme 4-7

An interesting application of allyltributyltin is Mizuno's double vicinal carbon-carbon bond-forming reaction on electron-deficient alkenes by allyltributyltin and alkyl iodide, as shown in Scheme 4-8.[91] The mixture of dicyano alkene **282**, allyltributyltin **29** and iodomethane **283** in 1:2:5 ratio was refluxed in benzene. The reaction was complete in 6 hours, affording **284** as the sole product in 85% yield. The allyl unit from allyltributyltin was regioselectively introduced to the α-carbon of dicyanoethene **282**, and the methyl group from iodomethane **283** to the β-carbon. This three-component coupling reaction inserted two different carbon-functional groups across a double bond in one step.



Scheme 4-8

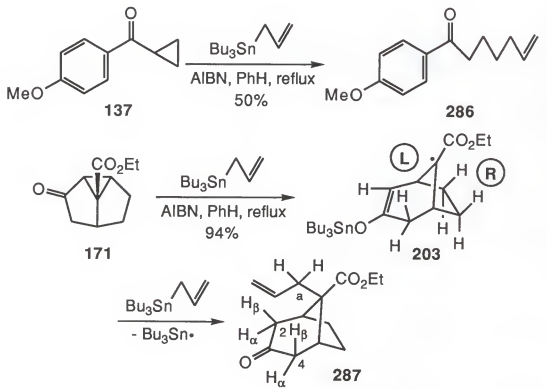
In order to expand the application scope of O-stannyl ketyl-promoted cyclopropane fragmentations, allyltributyltin chemistry was combined with our cyclopropane fragmentation studies. The allyltributyltin-induced cyclopropane fragmentation was unknown prior to the work described in this chapter. This fragmentation-allylation reaction is illustrated in Scheme 4-9. The primary process is AIBN-initiated formation of tributyltin radical **5** from allyltributyltin **29**. Radical **5** adds to the carbonyl of cyclopropyl ketone **130**, giving O-stannyl ketyl species **131**. The cyclopropane fragments to afford radical **132**. This intermediate attacks allyltributyltin **29** to acquire its allyl unit through an S_H2' substitution and regenerate tributyltin radical **5** to continue the chain reaction. Fragmentation-allylation product **285** is thus produced.



Scheme 4-9

To examine this fragmentation-allylation reaction, ketones **137** and **171** were refluxed with allyltributyltin and AIBN in benzene. The desired fragmentation-allylation products **286** (50%) and **287** (94%) were isolated, as

shown in Scheme 4-10. These are the first allyltributyltin-induced cyclopropane fragmentation-allylation reactions.



Scheme 4-10

The stereochemistry of **287** was assigned on the basis of the structure of **204L** (Figure 2-8) and was confirmed by NOE (nuclear Overhauser effect) difference NMR spectrum.[92] Positive NOE difference was observed for the b-protons at C2 and C4 methylenes when the allylic methylene (C_a) protons were irradiated. Excellent stereoselectivity in the allyl abstraction from allyltributyltin was achieved for radical intermediate **203**. This stereoselectivity could be rationalized with the steric difference between the **L** face and the **R** face of **203** for approaching allyltributyltin molecule.

In a summary, the O-stannyl ketyl-promoted cyclopropane fragmentation-allylation works well using allyltributyltin. This reaction forms a new carbon-carbon bond by introducing an allyl unit.

The preliminary study described in this chapter exhibits the duality of the free radical and tin(IV) enolate species generated in the O-stannyl ketyl-promoted cyclopropane fragmentations. Obviously, further synthetic efforts to capitalize on both species will definitely lead to exciting developments in this area.

CHAPTER 5
SUMMARY

The studies described in this dissertation are an attempt to expand the realm of free radical chemistry. The mild reaction conditions and the ability to control the reactivity, stereoselectivity and regioselectivity in these reactions have made free radical methodologies valuable and indispensable in organic synthesis. Much current free radical chemistry has been dominated by halogen and group abstractions as the source of organic radicals. The halogen or group functionality is usually lost in these classical free radical reactions. The reaction of TBTH and carbonyls provides a unique O-stannyl ketyl radical, which behaves like a pseudo-protected α-oxygen-functionalized radical. The original oxygen functionality is well preserved in its reactions, leading to alcohols or ketones. It makes O-stannyl ketyl radical especially attractive and provides advantages over classical free radicals. However, the O-stannyl ketyl chemistry is not well-understood yet, and its synthetic applications are still limited. The goal of this dissertation is to enhance our understanding of this ketyl species by studying the cyclopropane fragmentations and their synthetic applications.

Chapter 2 examined the O-stannyl ketyl-promoted cyclopropane fragmentations using a variety of cyclopropyl ketone precursors. The fragmentations were governed by both stereoelectronic effects and relative stability of the fragmentation radical products. The significance of radical-stability effects depended on the substitution pattern of the cyclopropane. These

studies enabled us to design synthetic methodologies to utilize the special merits of cyclopropane fragmentations.

Chapter 3 demonstrated our O-stannyl ketyl-promoted cyclopropane fragmentation-cyclization tandem sequence. This was the first synthetic application of O-stannyl ketyl-promoted cyclopropane fragmentations. Triquinane terpenes had been among the most interesting and challenging natural products for synthetic chemists for over two decades. Their unique *cis,trans,cis* angularly- or linearly-fused tricyclopentanoid skeletons had served as a testing vehicle for a wide variety of synthetic methodologies. The cyclopropane fragmentation-cyclization sequence was examined in the synthesis of a model angular triquinane and a model linear triquinane. The synthesis was successful and efficient. Very good regioselectivity and stereoselectivity were accomplished in both tandem sequences. This study demonstrated a novel synthetic route to triquinane compounds.

Chapter 4 reported preliminary results of two new investigations. The tin(IV) enolate formed in the cyclopropane fragmentations was examined. Its aldol and alkylation reactions were accomplished in excellent yield. The reaction of allyltributyltin with cyclopropyl ketones was performed. The O-stannyl ketyl-promoted cyclopropane fragmentation-allylation was successful. These preliminary results added new depth to O-stannyl ketyl chemistry and the cyclopropane fragmentation methodologies.

Collectively, these studies have extended the understanding and applications of O-stannyl ketyl chemistry. This work has established the use of O-stannyl ketyl-promoted cyclopropane fragmentations in organic synthesis.

CHAPTER 6
EXPERIMENTAL

General Methods

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). ^{1}H NMR spectra were recorded on a Varian Gemini-300 (300 MHz) or a General Electric QE-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the above-mentioned spectrometers. Chemical shifts are reported in ppm down field relative to tetramethylsilane as an internal standard in $CDCl_3$. Elemental analysis was performed by the Atlantic Microlab Inc., Norcross, Georgia or by the Elemental Analysis Service at the Department of Chemistry, University of Florida, Gainesville, Florida. The high resolution mass spectroscopy (HRMS) was performed by the Mass Spectroscopy Service at the Department of Chemistry, University of Florida, Gainesville, Florida.

All reactions were run under inert atmosphere of argon using oven dried apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography (TLC) and NMR spectroscopy. Solvents were dried according to established procedures by distillation under inert atmosphere from appropriate drying agents.

Analytical TLC was performed with Aldrich Z12272-6 precoated silica gel plates (0.25 mm) using 254 nm UV light, *p*-anisaldehyde in ethanol with acetic acid or phosphomolybdic acid in ethanol as indicator. Column chromatography

was performed using Merck silica gel 60 (230-400 mesh) by standard flash chromatographic techniques. GC experiments were performed on a Varian 3500 capillary gas chromatograph using a J & W fused silica capillary column (DB5-30W; film thickness 0.25 μ).

Experimental Procedures and Results

1-Dodecen-3-ol (**141**). Decyl aldehyde (5.00 g, 32.1 mmol) was dissolved in THF (50 mL). This solution was chilled to -78°C. Vinylmagnesium bromide (1.0 M in THF, 65.0 mL, 65.0 mmol) was added to the solution dropwise through a syringe. The reaction was complete in 1 hour and quenched by ice chips and NH_4Cl (aq.). The mixture was extracted with ether. The ether phase was dried, rotovaped and subjected to flash column chromatography to give **141** (6.13 g, 100%) as a clear oil. Rf (1:4 ether/hexane) 0.31. ^1H NMR δ 5.86 (m, 1H), 5.20 (d, J=17 Hz, 1H), 5.08 (d, J=11 Hz, 1H), 4.08 (m, 1H), 2.00 (s, 1H), 1.52-1.50 (m, 2H), 1.27 (m, 10H), 0.90-0.83 (m, 7H); ^{13}C NMR δ 141.4, 114.3, 73.2, 37.0, 31.9, 29.5 (3C), 29.3, 25.3, 22.6, 14.0. Anal. Calcd for $C_{12}H_{24}O$: C, 78.18; H, 13.13. Found: C, 78.38; H, 13.16.

1,6*E*-Dodecadien-3-ol (**142**). *Trans*-4-Decenal (1000 mg, 6.49 mmol) was dissolved in THF (13 mL). This solution was chilled to -78°C. Vinylmagnesium bromide (1.0 M in THF, 13.0 mL, 13.0 mmol) was added to the solution dropwise with a syringe. The reaction was complete in 1 hour and quenched by ice chips and NH_4Cl (aq.). The mixture was extracted with ether. The ether phase was dried, rotovaped and chromatographed to afford **142** (1194 mg, 100%) as a clear oil. Rf (1:4 ether/hexane) 0.37. ^1H NMR δ 5.86 (m, 1H), 5.43 (m, 2H), 5.22 (d, J=17 Hz, 1H), 5.10 (d, J=10 Hz, 1H), 4.11 (m, 1H), 2.11-2.05 (m, 2H), 1.97 (m, 2H), 1.86 (d, J=4.5 Hz, 1H), 1.58 (m, 2H), 1.39-1.28 (m, 6H),

0.88 (t, J=7 Hz, 3H); ^{13}C NMR δ 141.1, 131.2, 129.3, 114.5, 72.6, 36.7, 32.5, 31.3, 29.2, 28.5, 22.5, 14.0. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.11; H, 12.18.

Preparation of 1-Dodecen-3-one (**143**) by Swern oxidation.[48] Oxalyl chloride and DMSO were freshly distilled. Oxalyl chloride (2.09 mL, 23.9 mmol) was dissolved in CH_2Cl_2 (24 mL) in a 3-necked flask and chilled to -60°C. Through an additional funnel, a solution of DMSO (3.70 mL, 52.2 mmol) in CH_2Cl_2 (14 mL) was carefully dripped to the flask to maintain the inside temperature at -60°C. The reaction mixture was then stirred for 15 minutes. A solution of allyl alcohol **141** (2000 mg, 10.9 mmol) in CH_2Cl_2 (11 mL) was dropwise added to the flask through the additional funnel to maintain the inside temperature constantly at -60°C. The reaction mixture was stirred for 30 minutes. Triethylamine (7.6 mL, 54.3 mmol) was added to the flask. After 5 minutes, the chilling bath was removed to allow the reaction mixture to warm up gradually. Water was added to quench reaction. The mixture was extracted multiply with CH_2Cl_2. The organic phase was washed with water, dried and rotovaped. The residue was subjected to flash column chromatography to yield **143** (1030 mg, 52%) as a clear oil. Rf (1:3 ether/hexane) 0.56. ^1H NMR δ 6.36 (m, 1H), 6.21 (d, J=18 Hz, 1H), 5.80 (d, J=11 Hz, 1H), 2.58 (t, J=7.5 Hz, 2H), 1.62 (m, 2H), 1.27 (m, 12H), 0.88 (t, J=6 Hz, 3H); ^{13}C NMR δ 200.9, 136.5, 127.6, 39.6, 31.8, 29.3 (2C), 29.2 (2C), 23.9, 22.6, 14.0. HRMS for $C_{12}H_{22}O$ M+H, calcd: 183.1749. Found: 183.1743.

Preparation of 1-Dodecen-3-one (**143**) by Tsuji's allyl methyl carbonate method.[49] A mixture of allylic alcohol **141** (1000 mg, 5.42 mmol), allyl methyl carbonate (1234 μL, 10.88 mmol), catalyst $RuH_2(PPh_3)_4$ (62 mg, 0.054 mmol) and toluene (26 mL) was refluxed for 12 hours. Toluene was then rotovaped

away. The dark residue was chromatographed to afford **143** (833 mg, 83%) as a clear oil. Rf (1:3 ether/hexane) 0.56.

Preparation of 1,6*E*-Dodecadien-3-one (**144**) by Swern oxidation.[48] Oxalyl chloride (2.11 mL, 24.2 mmol) was dissolved in CH_2Cl_2 (24 mL) in a 3-necked flask and chilled to -60°C. A solution of DMSO (3.74 mL, 52.8 mmol) in CH_2Cl_2 (14 mL) was carefully dripped to the flask through an additional funnel, to maintain the inside temperature at -60°C. The reaction mixture was then stirred for 15 minutes. A solution of allyl alcohol **142** (2000 mg, 11.0 mmol) in CH_2Cl_2 (11 mL) was dropwise added to the flask through the additional funnel to maintain the inside temperature constant. The reaction mixture was stirred for 30 minutes. Triethylamine (7.7 mL, 55.0 mmol) was added to the flask. After 5 minutes, the chilling bath was removed to allow the reaction mixture to warm up gradually. Water was added to quench to reaction. The mixture was extracted multiply with CH_2Cl_2. The organic phase was washed with water, dried and rotovaped. The residue was chromatographed to give **144** (1037 mg, 52%) as a clear oil. Rf (1:3 ether/hexane) 0.47. ^{1}H NMR δ 6.36 (m, 1H), 6.21 (d, J=17 Hz, 1H), 5.82 (d, J=10 Hz, 1H), 5.43 (m, 2H), 2.65 (t, J=7 Hz, 2H), 2.31 (m, 2H), 1.96 (m, 2H), 1.33-1.27 (m, 6H), 0.88 (t, J=6 Hz, 3H); ^{13}C NMR δ 200.2, 136.5, 131.6, 128.2, 127.8, 39.5, 32.4, 31.3, 29.1, 26.9, 22.5, 14.0. HRMS for $C_{12}H_{20}O$, calcd: 180.1514. Found: 180.1513. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.70; H, 11.22.

Preparation of 1,6*E*-Dodecadien-3-one (**144**) by Tsuji's allyl methyl carbonate method.[49] A mixture of allylic alcohol **142** (1000 mg, 5.49 mmol), allyl methyl carbonate (1247 μL, 10.98 mmol), catalyst $RuH_2(PPh_3)_4$ (63 mg, 0.055 mmol) and toluene (28 mL) was refluxed for 12 hours. The mixture was rotovaped to remove toluene. The dark residue was chromatographed to afford **144** (683 mg, 69%) as a clear oil. Rf (1:3 ether/hexane) 0.47.

Preparation of 1-cyclopropyldecan-1-one (**135**) by Scheme 2-2. NaH (60%, 57 mg, 1.43 mmol) was placed in a Schlenk flask, washed with n-pentane (x3) and pumped. Trimethyloxosulfonium iodide (315 mg, 1.43 mmol) was added. DMSO (2 mL) was dripped to the stirred solid mixture through a syringe. After hydrogen evolution, a milky solution turned clear and was stirred for 15 minutes. Ketone **143** (200 mg, 1.10 mmol) in 1 mL DMSO was added. The mixture was stirred for 12 hours and quenched with water. The mixture was extracted with ether. The ether layer was dried, rotovaped, and chromatographed to give **135** (39 mg, 18%) as an oil. Rf (1:3 ether/hexane) 0.70. ^{1}H NMR δ 2.48 (t, J=7 Hz, 2H), 1.87 (m, 1H), 1.55 (m, 2H), 1.21 (m, 12H), 0.94 (m, 2H), 0.82-0.77 (m, 5H); ^{13}C NMR δ 211.1, 43.4, 31.8, 29.4 (2C), 29.2 (2C), 24.0, 22.6, 20.2, 14.0, 10.4 (2C). HRMS for $C_{13}H_{24}O$, calcd: 196.1827. Found: 196.1894.

Preparation of 1-cyclopropyl-4*E*-decen-1-one (**136**) by Scheme 2-2. NaH (60%, 130 mg, 3.25 mmol) was placed in a Schlenk flask, washed with n-pentane (x3) and pumped. Trimethyloxosulfonium iodide (715 mg, 3.25 mmol) was added. DMSO (11 mL) was dripped to the stirred solid mixture through a syringe. After hydrogen evolution, a milky solution turned clear and was stirred for 15 minutes. Ketone **144** (450 mg, 2.50 mmol) in 1 mL DMSO was added. The mixture was stirred for 12 hours and quenched with water. The mixture was extracted with ether. The ether layer was dried, rotovaped and subjected to column chromatography to give **136** (115 mg, 24%) as a clear oil. Rf (1:3 ether/hexane) 0.71. ^{1}H NMR δ 5.38 (m, 2H), 2.57 (t, J=7 Hz, 2H), 2.25 (q, J=7 Hz, 2H), 1.95-1.85 (m, 3H), 1.34-1.24 (m, 6H), 0.97 (m, 2H), 0.87-0.79 (m, 5H); ^{13}C NMR δ 210.3, 131.4, 128.3, 43.2, 32.4, 31.2, 29.1, 26.9, 22.4, 20.2, 13.9, 10.4 (2C). HRMS for $C_{13}H_{22}O$ M+H, calcd: 195.1749. Found: 195.1764.

1-Cyclopropyldecan-1-ol (**145**). Magnesium turning (185 mg, 7.69 mmol) was finely ground in a dry mortar and placed in a 3-necked flask equipped with a

condenser, an additional funnel and a stirring bar. A bit of iodine crystal was added to the turning. Cyclopropyl bromide (308 μL, 3.85 mmol) was dissolved in 4 mL THF and added into the additional funnel. About one third of the solution was dripped to the stirred turning. When the reaction started releasing heat and bubbles, the remaining cyclopropyl bromide solution was added dropwise. The mixture was heated in 65°C oil bath for 20 minutes. At room temperature, aldehyde **139** (200 mg, 1.28 mmol) was added. The mixture was stirred for 1 hour and quenched with NH_4Cl (aq.). The mixture was extracted with ether. The ether layer was dried, rotovaped and chromatographed to yield **145** (193 mg, 76%) as an oil. Rf (1:1 ether/hexane) 0.59. ^1H NMR δ 2.78 (m, 1H), 1.93 (s, 1H), 1.51 (m, 2H), 1.41-1.20 (m, 15H), 0.81 (t, J=7 Hz, 3H), 0.42 (m, 2H), 0.16 (m, 2H); ^{13}C NMR δ 76.7, 37.2, 31.8, 29.7, 29.5 (2C), 29.2, 25.7, 22.6, 17.8, 14.0, 2.6, 2.3. HRMS for $C_{13}H_{26}O$, calcd: 198.1984. Found: 198.1880.

1-Cyclopropyl-4*E*-decen-1-ol (**146**). Magnesium turning (187 mg, 7.79 mmol) was finely ground in a dry mortar and placed in a 3-necked flask equipped with a condenser, an additional funnel and a stirring bar. A bit of iodine crystal was added to the turning. Cyclopropyl bromide (312 μL, 3.90 mmol) was dissolved in 4 mL THF and added into the additional funnel. About one third of the solution was dripped to the stirred turning. When the reaction started releasing heat and bubbles, the remaining cyclopropyl bromide solution was added dropwise. The mixture was heated in 65°C oil bath for 20 minutes. At room temperature, aldehyde **140** (200 mg, 1.30 mmol) was added. The mixture was stirred for 1 hour and quenched with NH_4Cl (aq.). The mixture was extracted with ether. The ether layer was dried, rotovaped and chromatographed to afford **146** (178 mg, 70%) as an oil. Rf (1:1 ether/hexane) 0.58. ^1H NMR δ 5.36 (m, 2H), 2.81 (m, 1H), 2.07 (m, 2H), 1.91 (m, 3H), 1.60 (m, 2H), 1.22 (m, 6H), 0.82 (m, 4H), 0.43 (m, 2H), 0.18 (m, 2H); ^{13}C NMR δ 130.8, 129.7, 76.2, 37.0, 32.5,

31.3, 29.2, 28.8, 22.4, 17.8, 14.0, 2.6, 2.4. HRMS for $C_{13}H_{24}O$, calcd: 196.1827. Found: 196.1819.

Preparation of 1-cyclopropyldecan-1-one (**135**) by Scheme 2-4. Alcohol **136** (274 mg, 1.38 mmol) was dissolved in CH_2Cl_2 (3 mL). To this solution was added finely ground mixture of PCC (598 mg, 2.77 mmol) and silica gel (600 mg). The oxidation was complete in 4 hours and diluted with a large amount of ether. The ether solution was forced through a celite bed and the bed was rinsed with ether. The ether solution was rotovaped and chromatographed to yield **135** (224 mg, 83%) as an oil. Rf (1:3 ether/hexane) 0.70.

Preparation of 1-cyclopropyl-4*E*-decen-1-one (**136**) by Scheme 2-4. Alcohol **146** (150 mg, 0.765 mmol) was dissolved in CH_2Cl_2 (1.5 mL). To this solution was added finely ground mixture of PCC (330 mg, 1.53 mmol) and silica gel (330 mg). The oxidation was complete in 4 hours and diluted with a large amount of ether. The ether solution was forced through a celite bed and the bed was rinsed with ether. The ether solution was rotovaped and chromatographed to give **136** (116 mg, 78%) as an oil. Rf (1:3 ether/hexane) 0.71.

Phenyl(trans-2-phenylcyclopropyl)methanone (**138**). NaH (60%, 231 mg, 5.77 mmol) was placed in a 3-necked flask, washed with n-pentane (x3) and fully pumped. Trimethyloxosulfonium iodide (1270 mg, 5.77 mmol) was added. DMSO (10 mL) was dripped to the solid mixture through an additional funnel. After hydrogen evolution, a milky solution turned clear and was stirred for 15 minutes. *Trans*-chalcone **147** (1000 mg, 4.81 mmol) was added. The mixture was stirred for 20 hours and quenched with water. The mixture was extracted with ether. The ether layer was dried, rotovaped, and chromatographed to give **138** (1080 mg, 100%) as a white solid. Rf (1:3 ether/hexane) 0.48. ^1H NMR δ 8.01-7.98 (m, 2H), 7.59-7.56 (m, 1H), 7.49-7.43 (m, 2H), 7.35-7.29 (m, 2H), 7.25-7.22 (m, 1H), 7.21-7.17 (m, 2H), 2.91 (m, 1H), 2.70 (m, 1H), 1.93 (m, 1H), 1.56

(m, 1H); ^{13}C NMR δ 198.5, 140.5, 137.8, 132.9, 128.5 (4C), 128.1 (2C), 126.6 (2C), 126.2, 30.0, 29.3, 19.2. HRMS for $C_{16}H_{14}O$, calcd: 222.1045. Found: 222.1056.

Tridecan-4-one (**148**). A mixture of cyclopropyl ketone **135** (200 mg, 1.02 mmol), TBTH (549 μL, 2.04 mmol) and AIBN (84 mg, 0.51 mmol) in benzene (3 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C for 18 hours. A DBU workup procedure was used to remove excess TBTH and other tin byproducts.[34d,93] The reaction mixture was diluted with ether. Following addition of DBU (335 μL, 2.24 mmol) and 2-3 drops of water, an ethereal solution of iodine was added dropwise until the iodine orange color persisted. Rapid suction filtration through silica gel bed was performed. The silica gel bed was rinsed with ether, and the solution was concentrated and subjected to flash column chromatography to afford **148** (162 mg, 80%) as an oil. Rf (1:3 ether/hexane) 0.47. ^{1}H NMR 2.35 (m, 4H), 1.62-1.53 (m, 4H), 1.40-1.23 (m, 12H), 0.92-0.85 (m, 6H), identical to that published in Sadtler NMR Spectra (#23462);[94] ^{13}C NMR δ 211.6, 44.7, 42.8, 31.9, 29.4 (2C), 29.3 (2C), 23.9, 22.7, 17.3, 14.1, 13.8, identical to that published in Sadtler ^{13}C NMR Spectra (#5994).[95] HRMS for $C_{13}H_{26}O$, calcd: 198.1984. Found: 198.1987.

7*E*-Tridecen-4-one (**149**). A mixture of cyclopropyl ketone **136** (100 mg, 0.515 mmol), TBTH (277 μL, 1.03 mmol) and AIBN (42 mg, 0.258 mmol) in benzene (2 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C for 18 hours. The reaction mixture was rotovaped and subjected to flash column chromatography to give **149** (81 mg, 80%) as an oil. Rf (1:3 ether/hexane) 0.63. ^{1}H NMR δ 5.33 (m, 2H), 2.40-2.28 (m, 4H), 2.24-2.15 (m, 2H), 1.88 (m, 2H), 1.52 (m, 2H), 1.28-1.20 (m, 6H), 0.86-0.78 (m, 6H); ^{13}C NMR δ 210.8, 131.5, 128.3, 44.8, 42.6, 32.4, 31.3, 29.1, 26.8, 22.5, 17.2, 14.0, 13.7. HRMS for $C_{13}H_{24}O$, calcd: 196.1827. Found: 196.1808.

1-(4-Methoxyphenyl)-1-butanone (**150**). A mixture of cyclopropyl ketone **137** (200 mg, 1.14 mmol), TBTH (458 μL, 1.70 mmol) and AIBN (56 mg, 0.341 mmol) in benzene (2.5 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C for 2 hours. The reaction mixture was rotovaped and chromatographed to afford **150** (186 mg, 92%) as a solid. Rf (1:1 ether/hexane) 0.71. ^{1}H NMR δ 7.85 (d, J=9 Hz, 2H), 6.83 (d, J=9 Hz, 2H), 3.76 (s, 3H), 2.80 (t, J=7 Hz, 2H), 1.66 (m, 2H), 0.91 (t, J=7 Hz, 3H); ^{13}C NMR δ 198.7, 163.1, 130.0 (3C), 113.4 (2C), 55.2, 39.9, 17.8, 13.7. HRMS for $C_{11}H_{14}O_2$, calcd: 178.0994. Found: 178.0993.

1,4-Diphenylbutan-1-one (**151**). A mixture of compound **138** (200 mg, 0.901 mmol), TBTH (727 μL, 2.70 mmol) and AIBN (148 mg, 0.901 mmol) in benzene (4.5 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C for 5 hours. Quenched with ethanol, the reaction mixture was rotovaped and chromatographed to afford **151** (173 mg, 86%) as a clear liquid which slowly solidified. Rf (1:3 ether/hexane) 0.42. ^{1}H NMR δ 7.90-7.87 (m, 2H), 7.52-7.46 (m, 1H), 7.41-7.36 (m, 2H), 7.29-7.23 (m, 2H), 7.19-7.14 (m, 3H), 2.92 (t, J=7 Hz, 2H), 2.69 (t, J=7 Hz, 2H), 2.05 (m, 2H); ^{13}C NMR δ 199.8, 141.5, 136.9, 132.7, 128.4 (2C), 128.3 (2C), 128.2 (2C), 127.8 (2C), 125.8, 37.5, 35.0, 25.5. HRMS for $C_{16}H_{16}O$, calcd: 224.1201. Found: 224.1225.

3-Methoxycarbonyl-2-cyclohexen-1-one(**159**).[52] This synthetic work was identical to that described by Lange and Otulakowski.[52] A 3-necked flask equipped with an additional funnel, a condenser and a thermometer was used. Cyclohexanecarboxylic acid **156** (25.0 g, 195 mmol) was placed in the flask. Freshly distilled thionyl chloride (17.4 mL, 238 mmol) was dropwise added through the additional funnel in 30 minutes. This mixture was refluxed for 2 hours. Red phosphorus (310 mg, 10.0 mmol) was added with stirring. The temperature was increased to 90°C and bromine (12.3 mL, 238 mmol) was

dropwise added in 1.5 hour as the temperature was maintained below 105°C. The mixture was heated at 100°C for an additional hour and then chilled to 5°C. Anhydrous methanol (40 mL, 989 mmol) was dropwise added. The mixture was refluxed for 15 minutes, cooled, and poured into ice-cold water. The mixture was extracted with ether. The organic phase was washed with 1M $Na_2S_2O_3$ and saturated $NaHCO_3$ aqueous solutions, dried and rotovaped. The residue was distilled to give ester **157** (38.4 g, 89%). A solution of ester **157** (20.0 g, 90.5 mmol) and distilled quinoline (17.1 mL, 145 mmol) was refluxed for 1 hour. The mixture was cooled to room temperature, treated with 20% HCl (100 mL) and extracted with ether. The organic extract was washed with 10% HCl, water and saturated $NaHCO_3$ (aq.). This extract was dried, rotovaped and chromatographed to give **158** (12.6 g, 99%). Compound **158** (5.00 g, 35.8 mmol) was dissolved in benzene (50 mL) and stirred. To this solution was dropwise added a mixture of CrO_3 (10.0 g, 100 mmol) in acetic anhydride (25 mL) and glacial acetic acid (50 mL) over 30 minutes. After stirring for additional 20 minutes, benzene (50 mL) was added to dilute the reaction mixture. Chilled by ice, this acidic mixture was slowly neutralized with saturated KOH aqueous solution. The mixture was extracted with ether. The extract was washed with water, dried, rotovaped and chromatographed to afford **159** (2.81 g, 52%) as a clear oil. Rf (2:1 ether/hexane) 0.48. ^1H NMR δ 6.73 (t, J=2 Hz, 1H), 3.84 (s, 3H), 2.60 (dt, J=6 Hz, 2 Hz, 2H), 2.46 (m, 2H), 2.07 (m, 2H); ^{13}C NMR δ 199.6, 166.8, 148.6, 132.9, 52.4, 37.5, 24.7, 22.0. HRMS for $C_8H_{10}O_3$, calcd: 154.0630. Found: 154.0650.

6-Methoxycarbonylbicyclo[4.1.0]heptan-2-one (**153**). NaH (60%, 57 mg, 1.43 mmol) was placed in a 3-necked flask, washed with n-pentane (x3) and pumped to dry. Trimethyloxosulfonium iodide (315 mg, 1.43 mmol) was added. DMSO (2 mL) was dripped to the solid mixture through an additional funnel.

After hydrogen evolution, a milky solution turned clear and was stirred for 15 minutes. Compound **159** (200 mg, 1.30 mmol) in DMSO (1 mL) was added. The mixture was stirred overnight and quenched with water. The mixture was extracted with ether and the ether layer was dried, rotovaped, and chromatographed to give **153** as an oil (76 mg, 35%). Rf(2:1 ether/hexane) 0.37. ^{1}H NMR δ 3.71 (s, 3H), 2.39-2.17 (m, 4H), 2.13-2.01 (m, 1H), 1.87-1.79 (m, 1H), 1.72-1.67 (m, 1H), 1.64-1.54 (m, 2H); ^{13}C NMR δ 205.3 (s), 173.0 (s), 52.1 (q), 36.4 (t), 33.6 (d), 28.7 (s), 22.3 (t), 18.0 (t), 16.7 (t). HRMS for $C_9H_{12}O_3$ M+H, calcd: 169.0865. Found: 169.0849.

5,5-Diphenylbicyclo[4.1.0]heptan-2-one **(154).** NaH (60%, 39 mg, 0.968 mmol) was placed in a 3-necked flask, washed with n-pentane (x3) and pumped to dry. Trimethyloxosulfonium iodide (213 mg, 0.968 mmol) was added. DMSO (2 mL) was dripped to the solid mixture through an additional funnel. After hydrogen evolution, a milky solution turned clear and was stirred for 15 minutes. 4,4-Diphenyl-2-cyclohexen-1-one **160** (200 mg, 0.806 mmol) was added and the mixture was stirred overnight. The reaction was quenched with water and extracted with ether. The ether layer was dried, rotovaped and chromatographed to give **154** as a white solid (171 mg, 81%). Rf (ether) 0.65. IR (KBr) 1681; ^{1}H NMR δ 7.38-7.17 (m, 10H), 2.55-2.42 (m, 1H), 2.33-2.11 (m, 4H), 1.89-1.76 (m, 1H), 1.41-1.35 (m, 1H), 1.21-1.13 (m, 1H); ^{13}C NMR δ 207.3 (s), 148.3 (s), 146.3 (s), 128.3 (d), 128.2 (d), 127.7 (d), 126.7 (d), 126.4 (d), 126.2 (d), 44.5 (s), 33.5 (t), 28.5 (d), 27.9 (t), 27.6 (d), 10.0 (t). HRMS for $C_{19}H_{18}O$ M+H, calcd: 263.1436. Found: 263.1441.

Tricyclic ketone **155**. NaH (60%, 320 mg, 8.00 mmol) was placed in a 3-necked flask, washed with n-pentane (x3) and pumped to dry. Trimethyloxosulfonium iodide (1760 mg, 8.00 mmol) was added. DMSO (10 mL) was dripped to the solid mixture through an additional funnel. After hydrogen evolution, a milky

solution turned clear and was stirred for 15 minutes. (-)-Verbenone **161** (1000 mg, 6.67 mmol) in DMSO (5 mL) was added. This mixture was stirred for 24 hours. The reaction was quenched with water and extracted with ether. The ether layer was dried, rotovaped and chromatographed to give **155** (1187 mg, 100%) as a clear oil. Rf (1:2 ether/hexane) 0.49; Rf (1:1 ether/hexane) 0.58. ^{1}H NMR δ 2.26-2.21 (m, 1H), 2.19-2.14 (m, 2H), 1.61 (m, 1H), 1.48 (m, 1H), 1.32 (d, J=1.2 Hz, 3H), 1.30 (m, 1H), 1.17 (d, J=1.2 Hz, 3H), 1.01 (d, J=0.9 Hz, 3H), 0.77 (m, 1H); ^{13}C NMR δ 209.5, 57.8, 49.5, 45.4, 30.5, 26.0, 22.7, 22.0, 21.8, 21.7, 21.5. HRMS for $C_{11}H_{16}O$ M+H, calcd: 165.1279. Found: 165.1300.

4-Methoxycarbonylcycloheptanone (165). A mixture of **153** (40 mg, 0.238 mmol), TBTH (192 μL, 0.714 mmol) and AIBN (40 mg, 0.238 mmol) in benzene (2.5 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C for 2 hours. Quenched with ethanol, the reaction mixture was rotovaped and chromatographed to give **165** as an oil (28 mg, 69%). Rf (2:1 ether/hexane) 0.38. IR (KBr) 1734, 1700; ^{1}H NMR δ 3.70 (s, 3H), 2.66-2.46 (m, 4H), 2.18-2.04 (m, 2H), 2.02-1.76 (m, 3H), 1.73-1.59 (m, 2H); ^{13}C NMR δ 213.4 (s), 175.4 (s), 51.7 (q), 46.3 (d), 43.4 (t), 41.5 (t), 32.5 (t), 26.3 (t), 22.4 (t). These NMR spectra were identical to those reported by Cossy.[55]

3-Methyl-4,4-diphenylcyclohexanone (166). A mixture of **154** (84 mg, 0.321 mmol), TBTH (173 μL, 0.642 mmol) and AIBN (53 mg, 0.321 mmol) in benzene (3.2 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C for 2.5 hours. Quenched with ethanol, the reaction mixture was rotovaped and chromatographed to give **166** as a white solid (73 mg, 86%). Rf (ether) 0.71. ^{1}H NMR δ 7.55-7.08 (m, 10H), 3.37-3.32 (m, 1H), 2.98-2.86 (m, 2H), 2.70 (m, 1H), 2.41-2.38 (m, 1H), 2.36-2.25 (m, 2H), 0.81 (d, J=7 Hz, 3H); ^{13}C NMR δ 210.9 (s), 146.8 (s), 145.0 (s), 128.9 (d), 128.3 (d), 126.8 (d), 126.5 (d), 126.2 (d), 125.7 (d), 48.2 (s), 45.7 (t), 38.4 (t), 37.7 (d), 29.6 (t), 16.7 (q).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.31; H, 7.63. Found: C, 86.27; H, 7.85. HRMS for $C_{19}H_{20}O$ M+H, calcd: 265.1592. Found: 265.1598.

Bicyclic ketone **167**. A mixture of ketone **155** (200 mg, 1.22 mmol), TBTH (656 μL, 2.44 mmol) and AIBN (80 mg, 0.49 mmol) in benzene (4 mL) was degassed by argon stream for 15 minutes. The mixture was refluxed at 80°C overnight. Quenched with ethanol, the reaction mixture was rotovaped and chromatographed to give **167** as a clear oil (86 mg, 76%). Rf (1:1 ether/hexane) 0.66. ^{1}H NMR δ 2.54 (m, 2H), 2.37 (d, J=2 Hz, 2H), 1.88 (t, J=6 Hz, 1H), 1.64 (d, J=10 Hz, 1H), 1.36 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H); ^{13}C NMR δ 214.5, 58.1, 53.6, 48.2, 41.1, 32.0, 31.8, 29.0, 27.2, 25.7, 25.4. HRMS for $C_{11}H_{18}O$, calcd: 166.1358. Found: 166.1366.

(Ethoxycarbonylmethyl)triphenylphosphonium bromide (**183**). In an Erlenmeyer flask, triphenylphosphine (131 g, 0.5 mol) was dissolved in benzene (250 mL). This solution was stirred vigorously while ethyl bromoacetate (83.5 g, 0.5 mol) was added dropwise. A white precipitate formed immediately. After 3 hours the white precipitate was collected by a Büchner funnel and washed with cold benzene (250 mL) and cold pentane (200 mL). The white solid then was pumped overnight to dry. Compound **183** (213 g, 99.3% yield) was thus obtained. ^{1}H NMR δ 7.91-7.70 (m, 12H), 7.50-7.35 (m, 3H), 5.49 (m, 2H), 4.03 (m, 2H), 1.06 (m, 3H); ^{13}C NMR δ 164.4, 135.1 (3C), 133.9 (3C), 133.8 (3C), 130.3 (3C), 130.1 (3C), 128.2 (3C), 117.824 ($J_{31P-13C}$=89 Hz for this doublet), 62.8, 33.1 ($J_{31P-13C}$=57 Hz for this doublet), 13.6. HRMS for $C_{22}H_{22}O_2P$, calcd: 349.1357. Found: 349.1358.

Ethyl allenecarboxylate (**180**).[66] This synthetic work was identical to that described by Lang and Hansen.[66] In a 3-necked flask, Wittig salt **183** (30 g, 70 mmol) was dissolved in CH_2Cl_2 (280 mL) at room temperature. To this flask a solution of freshly distilled triethylamine (19.7 mL, 140 mmol) in CH_2Cl_2 (70

mL) was added in 5 minutes with an additional funnel. Then the solution of freshly distilled acetyl chloride (5.0 mL, 70 mmol) in 70 mL CH_2Cl_2 was added in 15 minutes. The reaction was monitored with TLC (stained in $KMnO_4$-NaOH aqueous solution). The reaction was completed in 1 hour. The reaction mixture was rotovaped to remove CH_2Cl_2. To the semi-solid residue was added 400 mL pentane. The slurry was then stirred for 2 hours. The precipitate was removed by a Büchner funnel and the pentane filtrate was rotovaped to 50 mL in volume. The precipitate was then again filtered with a Büchner funnel. Distillation of the filtrate under reduced pressure afforded **180** (470 mg, 17%) as colorless liquid, boiling point 82°C at 9.5 torr. Rf (1:1 hexane/ ether) 0.66. ^1H NMR δ 5.64 (t, 1H), 5.22 (d, 2H), 4.21 (q, 2H), 1.29 (t, 3H); ^{13}C NMR δ 215.6, 165.7, 88.0, 79.2, 60.9, 14.1.

2-Trimethylsilyloxy-1,3-cyclohexadiene (**185**).[68] This synthetic work was identical to that described by Rubottom and Grube.[68] THF (240 mL) was placed in a flask and chilled to -78°C. To this flask was added diisopropylamine (13.6 g, 0.135 mol) and n-butyl lithium (2.5M in hexane, 58.8 mL, 0.147 mol). After 30 minutes, 2-cyclohexen-1-one **178** (12.0 g, 0.122 mol) was dropwise syringed into the reaction flask over 5 minutes. After stirring at -78°C for 20 minutes, trimethylsilyl chloride (26.6 g, 0.245 mol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 2 hours before it was poured into an ice-cold stirred mixture of n-pentane (500 mL) and saturated $NaHCO_3$ aqueous solution (300 mL). After 10 minutes, the pentane phase was quickly separated, dried with $MgSO_4$, and rotovaped. Vacuum distillation of the residue afforded **185** (18.0 g, 87%) as a clear liquid, boiling point 100°C at 7.5 torr. IR (KBr) 3422, 1649, 1252, 1199. ^1H NMR δ 5.96 (m, 1H), 5.79 (m, 1H), 4.98 (m, 1H), 2.28-2.17 (m, 4H), 0.29 (s, 9H); ^{13}C NMR δ 148.1, 128.8, 126.5, 102.4, 22.6, 21.8, 0.2.

3,4-Dimethoxycarbonylphenol (**189**). 2-Trimethylsilyloxy-1,3-cyclohexadiene **185** (1000 mg, 5.88 mmol) and dimethyl acetylenedicarboxylate **186** (1250 mg, 8.82 mmol) were refluxed in 5 mL toluene at 120°C for 1 day. Then to the mixture was added 3 M HCl (5 mL). After stirring for 3 hours, the mixture was separated and the aqueous phase was multiply extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and rotovaped. Chromatographic purification of the residue gave **189** (1100 mg, 89%) as a white crystal. Rf (1:2 hexane/ether) 0.17; IR (KBr) 3410 (broad), 1638 (broad); ^1H NMR δ 7.74 (d, J=8.4 Hz, 1H), 7.01 (d, J=2.4 Hz, 1H), 6.92 (dd, J=8.4 Hz, 2.4 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR δ 169.6, 167.2, 159.3, 135.6, 131.9, 121.5, 117.3, 115.3, 53.0, 52.5. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.13; H, 4.80. Found: C, 57.15; H, 4.80.

Ethyl 4-hydroxybenzoate (**191**). In a flask **185** (200 mg, 1.18 mmol) and ethyl propiolate **190** (138 mg, 1.41 mmol) was refluxed in 1 mL toluene for 16 hours. The reaction was monitored with GC. To workup to the mixture was added 1N HCl and stirred for 4 hours. The mixture then was multiply extracted with ether. The ether phase was dried, rotovaped and chromatographed to give **191** (185 mg, 95%) as a white crystal. Melting point: 116-118°C. Rf (1:1 hexane/ether) 0.43. ^1H NMR δ 7.96 (m, 2H), 6.89 (m, 2H), 4.36 (q, J=7 Hz, 2H), 1.39 (t, J=7 Hz, 3H); ^{13}C NMR δ 167.4, 160.7, 131.9, 122.3, 115.3, 61.1, 14.2. Anal. Calcd for $C_9H_{10}O_3$: C, 65.04; H, 6.07. Found: C, 64.95; H, 6.08.

2,3-Dimethoxycarbonylbicyclo[2.2.2]oct-2-en-5-one (**177**). Diene **185** (10.7 g, 59.2 mmol) and dimethyl acetylenedicarboxylate **186** (10.1 g, 71.1 mmol) were refluxed in benzene (200 mL) at 80°C overnight. After benzene was rotovaped, to the residue was added ether (200 mL) and 6M HCl (20 mL). After stirring for 8 hours, the ether phase was separated. The aqueous layer was extracted with ether and ethyl acetate. The organic extracts were combined, dried and

rotovaped. Chromatographic purification of the residue afforded **177** (9.3 g, 61%) as a yellow thick oil. Rf (1:2 hexane/ether) 0.30. RI (KBr) 2954, 1723, 1636; ^{1}H NMR δ 3.72 (s, 3H), 3.70 (s, 3H), 3.63 (m, 1H), 3.43 (m, 1H), 1.68-1.88 (m, 4H); ^{13}C NMR δ 208.6, 166.0, 164.7, 143.4, 134.6, 52.4, 49.6, 38.8, 34.9, 24.0, 22.7. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.37; H, 6.08.

2-Ethoxycarbonylbicyclo[2.2.2]oct-2-en-5-one (**176**). In a flask **185** (15.0 g, 88.2 mmol), ethyl propiolate **190** (13.0 g, 132 mmol) and a few BHT (i.e. 2,6-di-t-butyl-4-methylphenol) crystals were refluxed in benzene (44 mL) at 70-75°C for 7 days. Then the reaction mixture was rotovaped to remove benzene and acidified by 1M HCl. After stirring overnight, the aqueous mixture was extracted with chloroform. The chloroform phase was dried, rotovaped and chromatographed to give **176** (15.1 g, 88%) as a colorless oil. Rf (ether) 0.67. ^{1}H NMR δ 7.20 (dd, J=7 Hz, 2 Hz, 1H), 4.24 (q, J=7 Hz, 2H), 3.62 (m, 1H), 3.35 (m, 1H), 2.07 (m, 2H), 1.84-1.56 (m, 4H), 1.33 (t, J=7 Hz, 3H); ^{13}C NMR δ 210.5, 164.0, 140.0, 138.0, 60.6, 49.6, 39.5, 31.9, 24.1, 22.5, 14.1. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.83; H, 7.40.

1,2-Dimethoxycarbonyltricyclo[3.3.0.0^{2,8}]octan-3-one (**174**). Octenone **177** (180 mg, 0.76 mmol) was dissolved in acetone (9.6 mL) in a Pyrex tube. The solution was degassed with dry nitrogen stream for 30 minutes and then stirred under direct irradiation of a 450W Hanovia lamp for 24 hours. The reaction mixture was rotovaped and chromatographed to give **174** (150 mg, 83%) as a clear thick oil. Rf (2:1 ether/hexane) 0.37. IR (KBr) 2955, 1720 (broad),1637 (weak); ^{1}H NMR δ 3.75 (s, 3H), 3.72 (s, 3H), 3.46 (m, 1H), 3.14 (d, J=6 Hz, 1H), 2.74 (m, 1H), 2.25 (m, 2H), 1.96 (d, J=18 Hz, 1H), 1.65 (m, 2H); ^{13}C NMR δ 207.0 (s) 169.5 (s), 165.2 (s), 57.3 (s), 56.1 (s), 52.7 (q), 52.3 (q), 47.5 (t), 41.8

(d), 39.8 (t), 38.6 (d), 24.7 (t). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.43, H, 6.08.

Preparation of **174** using acetophenone as the triplet sensitizer and solvent. Octenone **177** (400 mg, 1.67 mmol) was dissolved in acetophenone (20 mL) in a Pyrex tube. The solution was degassed with dry nitrogen stream for 30 minutes and then stirred under direct irradiation of a 450W Hanovia lamp for 12 hours. The reaction mixture was distilled at 1.5 torr to remove acetophenone (boiling point 83-86°C at 1.5 torr). The residue was chromatographed to give **174** (364 mg, 92%) as a clear thick oil. Rf (2:1 ether/hexane) 0.37.

1-Ethoxycarbonyltricyclo[3.3.0.0^{2,8}]octan-3-one (**173**). Octenone **176** (316 mg, 1.61 mmol) was dissolved in acetone (20 mL) in a Pyrex tube. The solution was degassed with dry nitrogen stream for 30 minutes and stirred under irradiation of a 450W Hanovia lamp for 24 hours. The reaction mixture then was rotovaped and chromatographed to produce **173** as a colorless oil (265 mg, 84%). This reaction was repeated with the solution of octenone **176** (15.1 g, 77.8 mmol) in acetone (970 mL) irradiated for 48 hours. The yield for **173** was increased to 88% (13.3 g). Rf (ether) 0.67. IR (KBr) 2957, 1724, 1624 (weak); ^{1}H NMR δ 4.17 (q, J=7 Hz, 2H), 3.42 (m, 1H), 2.71-2.58 (m, 3H), 2.23 (m, 2H), 1.83 (d, J=18 Hz, 1H), 1.65 (m, 2H), 1.27 (t, J=7 Hz, 3H); ^{13}C NMR δ 211.7 (s), 171.3 (s), 60.7 (t), 49.8 (s), 47.6 (d), 46.9 (t), 40.6 (t), 38.9 (d), 37.8 (d), 24.6 (t), 14.1 (q). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.88; H, 7.36.

1-*Tert*-Butyldiphenylsiloxymethyltricyclo[3.3.0.0^{2,8}]octan-3-ol (**199**). In a flask, tricyclic ketoester **173** (560 mg, 2.86 mmol) was dissolved in CH_2Cl_2 (7.2 mL) and chilled at -78°C. To this flask was dropwise added DIBAH (1.0 M solution in hexane, 14.3 mL, 14.3 mmol) by a syringe. The mixture was stirred at -78°C for 2 hours and then warmed up to room temperature. When the reaction was complete, it was quenched with methanol at -78°C. To this mixture was added

saturated sodium potassium tartrate (Rochelle's salt) aqueous solution and stirred overnight to clear up the aqueous layer. The mixture then was extracted with ethyl acetate. The acetate extract was dried and rotovaped to afford diol **198** (440 mg, 99%). Rf (ethyl acetate) 0.28. Without further purification diol **198** (420 mg, 2.73 mmol) was dissolved in pyridine (5.4 mL). At 0°C to this solution was added *tert*-butyldiphenylsilyl chloride (851 mL, 3.27 mmol). The mixture was stirred for 10 hours and quenched with water. The mixture then was rotovaped and pumped to remove pyridine. The residue was chromatographed to give **199** (393 mg, 37%) as a clear thick oil. Rf (1:2 hexane/ether) 0.53. ^{1}H NMR δ 7.71-7.65 (m, 4H), 7.39-7.32 (m, 6H), 4.78 (m, 1H), 3.79 (dd, J=27 Hz, 11 Hz, 2H), 2.64 (m, 1H), 2.51 (m, 1H), 2.31-1.79 (m, 4H), 1.57-1.45 (m, 1H), 1.38 (m, 1H), 1.27 (m, 1H), 1.06 (s, 9H); ^{13}C NMR δ 135.5 (d), 134.0 (s), 129.5 (d), 127.5 (d), 76.1 (d) and 73.0 (d), 65.9 (t) and 65.8 (t), 50.5 (s) and 49.2 (s), 46.7 (t), 45.1 (d) and 43.7 (d), 39.8 (t) and 39.7 (t), 38.6 (d) and 38.2 (d), 32.1 (d) and 29.1 (d), 26.9 (q) and 26.8 (q), 24.9 (t) and 23.6 (t), 19.2 (s). HRMS for $C_{25}H_{32}O_2Si$, calcd: 392.2172. Found: 392.2053.

1-*Tert*-Butyldiphenylsiloxymethyltricyclo[3.3.0.0^{2,8}]octan-3-one (**172**). PCC (420 mg, 1.94 mmol) was finely ground with Kieselgel silica gel 60 (420 mg, 1 weight equivalent) and the light orange powder was suspended in CH_2Cl_2 (4 mL). Tricyclic alcohol **199** (320 mg, 0.816 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to the PCC suspension. After 2 hours the reaction mixture was filtered through a celite bed in a Büchner funnel. The brown cake was washed with copious amount of ether. The filtrate was rotovaped and chromatographed to yield **172** (222 mg, 70%) as a clear thick oil. Rf (1:1 hexane/ether) 0.46. ^{1}H NMR δ 7.67-7.63 (m, 4H), 7.42-7.37 (m, 6H), 3.92 (dd, J=31 Hz, 11 Hz, 2H), 2.87 (m, 1H), 2.58 (m, 1H), 2.07 (m, 2H), 1.86 (m, 1H), 1.75 (d, J=18 Hz, 1H), 1.63-1.51 (m, 2H), 1.27 (m, 1H), 1.06 (s, 9H); ^{13}C NMR δ 214.8 (s), 135.4 (d), 133.5

(s), 129.7 (d), 127.6 (d), 64.3 (t), 51.9 (s), 47.2 (t), 43.2 (d), 39.9 (t), 39.5 (d), 34.4 (d), 26.8 (q), 25.3 (t), 19.2 (s). HRMS for $C_{25}H_{30}O_2Si$ M+H, calcd: 391.2093. Found: 391.2040. Anal. Calcd for $C_{25}H_{30}O_2Si$: C, 76.88; H, 7.74. Found: C, 76.73; H, 7.84.

1-*Tert*-Butyldiphenylsiloxymethylbicyclo[3.3.0]octan-3-one (**202**). To a solution of tricyclic ketone **172** (120 mg, 0.308 mmol) in benzene (3.1 mL) was added TBTH (250 mL, 0.923 mmol) and AIBN (50 mg, 0.308 mmol). The mixture was degassed with argon for 15 minutes and refluxed at 80°C for 4 hours. The reaction mixture was rotovaped and chromatographed to give **202** (89 mg, 83%) as a clear oil along with unreacted starting ketone **172** (13 mg). Rf (1:1 hexane/ether) 0.54. ^{1}H NMR δ 7.66-7.63 (m, 4H), 7.43-7.38 (m, 6H), 3.52 (m, 2H), 2.64 (m, 1H), 2.59-2.52 (m, 2H), 2.11 (m, 2H), 1.95 (m, 1H), 1.75-1.49 (m, 4H), 1.39 (m, 1H), 1.05 (s, 9H); ^{13}C NMR δ 219.6 (s), 135.6 (d), 135.6 (d), 133.4 (s), 133.3 (s), 129.7 (d), 129.7 (d), 127.7 (d), 70.4 (t), 52.5 (s), 48.2 (t), 45.4 (t), 42.7 (d), 36.3 (t), 34.1 (t), 26.9 (q), 24.8 (t), 19.3 (s). HRMS for $C_{25}H_{32}O_2Si$ M+H, calcd: 393.2250. Found: 393.2201. Anal. Calcd for $C_{25}H_{32}O_2Si$: C, 76.48; H, 8.22. Found: C, 76.32; H, 8.30.

8-Ethoxycarbonylbicyclo[3.2.1]octan-3-one (**204**). The mixture of tricyclic ketone **173** (112 mg, 0.571 mmol), TBTH (384 mL, 1.43 mmol) and AIBN (30 mg, 0.171 mmol) in benzene (5.7 mL) was degassed with argon for 15 minutes and refluxed at 80°C for 5 hours. The reaction mixture was rotovaped and chromatographed to afford **204** (106 mg, 94%) as a colorless oil. Rf (1:2 hexane/ether) 0.53. IR (KBr) 2956, 1709, 1642; ^{1}H NMR δ 4.22 (q, J=7 Hz, 2H), 2.80 (d, J=15 Hz, 2H), 2.77 (s, 3H), 2.24 (d, J=15 Hz, 2H), 1.89 (d, J=9 Hz, 2H), 1.73-1.55 (m, 2H), 1.30 (t, J=7 Hz, 3H); ^{13}C NMR δ 211.6 (s), 172.5 (s), 60.5 (t), 49.6 (d), 46.2 (2C, t), 36.6 (2C, d), 29.1 (2C, t), 14.3 (q). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.18; H, 8.34.

1,2-Dimethoxycarbonylbicyclo[3.3.0]octan-3-one (**206**/**206T**). To a solution of tricyclic ketone **174** (450 mg, 1.89 mmol) in benzene (20 mL) was added TBTH (1380 mg, 4.74 mmol) and AIBN (100 mg, 0.61 mmol). The mixture was degassed with argon stream for 15 minutes and refluxed at 80°C for 3 hours. The reaction mixture was rotovaped and chromatographed to yield **206**/**206T** (270 mg, 59%) as a clear thick oil. Rf (1/2 hexane/ether) 0.48. IR (KBr) 3427 (broad), 1729, 1664, 1626 (weak), 1286; ^{1}H NMR δ 10.55 (s, 0.8H), 3.78 (s, 3.0H), 3.70 (s, 3.0H), 2.93 (m, 1.1 H), 2.65 (m, 1.0H), 2.39 (m, 1.0 H), 2.26 (d, J=18 Hz, 1.1H), 1.50-2.10 (m, 7.6H), 1.40 (m, 1.0H), 1.26 (m, 0.5H), 0.90 (m, 0.5H); ^{13}C NMR δ 177.0 (s), 176.3 (s), 119.6 (s), 119.0 (s), 103.9 (s), 68.2 (s), 61.7 (s), 52.1 (q), 51.2 (q), 44.4 (d), 38.9 (t), 35.6 (t), 35.2 (t), 26.0 (t), 25.1 (d), 23.4 (d). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.87; H, 6.82.

2,4-Dinitrophenylhydrazone (**207**). In a dry flask, 2,4-dinitrophenylhydrazine (125 mg, 0.631 mmol) was dissolved in methanol (4 mL) with concentrate H_2SO_4 (0.2 mL), warmed by water bath. In another dry flask, bicyclic ketone **204** (100 mg, 0.510 mmol) was dissolved in methanol (5 mL). To this solution was dropwise added the dinitrophenylhydrazine solution. Orange precipitate formed immediately. After chilled in ice bath, the precipitate was collected by a Büchner funnel. This dark orange crude product was multiply recrystallized with ethanol-water. Clean product **207** (105 mg, 55%) was obtained as golden flakes. Melting point: 106-107.5°C. ^{1}H NMR δ 11.14 (s, 1H), 9.10 (d, J=2 Hz, 1H), 8.28 (dd, J=10 Hz, 2 Hz, 1H), 7.95 (d, J=10 Hz, 1H), 4.22 (q, J=7 Hz, 2H), 2.82 (d, J=15 Hz, 2H), 2.78 (s, 3H), 2.53 (m, 2H), 1.90 (m, 2H), 1.64 (m, 1H), 1.47 (m, 1H), 1.31 (t, J=7 Hz, 3H); ^{13}C NMR δ 196.1 (s), 172.3 (s), 158.1 (s), 145.1 (s), 139.6 (s), 129.8 (d), 123.4 (d), 116.3 (d), 60.4 (t), 49.8 (d), 38.3 (t), 36.1 (d), 35.4 (d), 31.8 (t), 29.6 (t), 28.3 (t), 14.3 (q). Anal. Calcd for $C_{17}H_{20}O_6N_4$: C, 54.25; H, 5.36; N, 14.89. Found: C, 54.15; H, 5.37; N, 14.93.

8-Ethoxycarbonyl-8-deuterobicyclo[3.2.1]octan-3-one (**204D**). A mixture of tricyclic ketone **173** (145 mg, 0.747 mmol), tributyltin deuteride (872 mg, 2.99 mmol) and AIBN (37 mg, 0.224 mmol) in benzene (1.5 mL) was degassed with argon stream for 15 minutes and refluxed at 80°C for 3 days. The reaction mixture was directly chromatographed to give recovered **173** (47 mg) and the cyclopropane fragmentation product **204D** (78 mg, 78%). Rf (1:1 ether/hexane) 0.68. ^{1}H NMR δ 4.15 (q, J=7 Hz, 2H), 2.72 (d, J=15 Hz, 2H), 2.68 (d, J=3.6 Hz, 2H), 2.17 (d, J=15 Hz, 2H), 1.84-1.80 (m, 2H), 1.51 (m, 2H), 1.23 (t, J=7 Hz, 3H); ^{13}C NMR δ 211.4, 172.4, 60.4, 49.1 (very weak, triplet, J=22 Hz), 46.1, 36.5, 28.9, 14.2. HRMS for $C_{11}H_{15}DO_3$ M+H, calcd: 198.1240. Found: 198.1239.

8-Ethoxycarbonyl-8-cyanoisopropylbicyclo[3.2.1]octan-3-one (**210**). A mixture of tricyclic ketone **173** (97 mg, 0.500 mmol), TBTH (1345 μL, 5.00 mmol) and AIBN (410 mg, 2.50 mmol) in benzene (5 mL) was degassed with argon stream for 15 minutes and refluxed at 80°C for 1 hour. The reaction mixture was rotovaped and directly chromatographed to afford **210** (136 mg) as a semi-solid. Rf (2:1 ether/hexane) 0.63. ^{1}H NMR δ 4.15 (q, J=7 Hz, 2H), 2.72 (d, J=15 Hz, 2H), 2.67 (d, J=4.5 Hz, 2H), 2.16 (d, J=15 Hz, 2H), 1.84-1.80 (m, 2H), 1.65 (s, 6H), 1.51 (m, 2H), 1.22 (t, J=7 Hz, 3H); ^{13}C NMR δ 211.1 (s), 172.3 (s), 118.9 (s), 68.0 (s), 60.3 (t), 46.0 (d), 36.4 (t), 28.9 (t), 24.9 (2C, q), 14.1 (q).

1,2-Dimethoxycarbonylbicyclo[3.3.0]oct-2-ene (**213**). Ketone **206/206T** (220 mg, 0.92 mmol) was dissolved in methanol (3 mL) and chilled to -78°C. To the solution was added sodium borohydride (140 mg, 3.67 mmol). After stirring for 3 hours, the reduction was quenched with water and multiply extracted with ethyl acetate. The organic extract was rotovaped to afford **211** (200 mg, 90%) as an oil. Rf (ether) 0.31. Crude **211** (200 mg, 0.83 mmol) and triethylamine (417 mg, 4.13 mmol) were dissolved in CH_2Cl_2 (2 mL) and chilled to -20°C. To this mixture was dropwise added mesyl (i.e. methanesulfonyl) chloride (188 mg,

1.65 mmol, in 2 mL CH_2Cl_2). After stirring for 1 hour, the reaction mixture was allowed to warm up to room temperature and stirred for 2 hours. The mixture was rotovaped to afford crude solid mesylate **212**. To the mesylate was added DBU (628 mg, 4.13 mmol) and THF (3 mL). This mixture was refluxed overnight. The reaction was quenched with water and extracted with ether. The ether extract was dried, rotovaped and chromatographed to give **213** (35 mg, 20%) as a clear oil. Rf (1:1 hexane/ether) 0.45. ^1H NMR δ 6.82 (m, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.83 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 1.94 (m, 2H), 1.75 (m, 2H), 1.68(m, 1H), 1.38 (m, 1H); ^{13}C NMR δ 176.6 (s), 164.6 (s), 144.8 (d), 137.6 (s), 65.7 (s), 52.2 (q), 51.5 (q), 49.4 (d), 39.7 (t), 35.6 (t), 35.4 (t), 26.1 (t). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.31.

1-Formyltricyclo[3.3.0.0^{2,8}]octane-3-one (**240**). Compound **173** (1705 mg, 8.79 mmol) was dissolved in CH_2Cl_2 (22 mL) at -78°C. To the solution was dropwise added DIBAH (1.0 M in hexane, 44 mL, 44 mmol) through a syringe. After stirring at -78°C for 1 hour, the dry ice bath was removed and the reaction mixture was allowed to warm up to room temperature. The reaction was complete overnight. The reaction then was chilled to -78°C and quenched with ethanol. To clear up the gray glue formed, at room temperature an aqueous solution of Rochelle's salt was added and the mixture was stirred vigorously for 2 hours. The mixture was multiply extracted with ethyl acetate. The ethyl acetate extracts were combined, dried and rotovaped to afford crude tricyclic diol **198** (1600 mg) as a thick oil. Without further purification, crude diol **198** was dissolved in CH_2Cl_2 (9 mL). PCC (9.50 g, 44 mmol) and silica gel (9.50 g) were finely ground in a mortar. The powder was suspended in CH_2Cl_2 (88 mL). This suspension was added to the stirred solution of diol **198** at room temperature. The oxidation was complete in 2 hours. Then the dark brown suspension was filtered through a celite bed in a Büchner funnel and the bed was rinsed with

copious amount of ether. The organic solution was then rotovaped and the residue was chromatographed to afford **240** (686 mg, 52%) as a thick oil which slowly solidified in refrigerator. Rf (ether) 0.57. IR (KBr) 3444, 2957, 2876, 1725, 1702, 1310, 1255, 1196, 1152, 1039; ^{1}H NMR δ 9.21 (s, 1H), 3.55-3.50 (m, 1H), 2.79 (t, J=10 Hz, 1H), 2.75-2.62 (m, 2H), 2.30-2.12 (m, 2H), 1.90 (d, J=18 Hz, 1H), 1.78-1.65 (m, 2H); ^{13}C NMR δ 210.6 (s), 196.2 (d), 60.2 (s), 47.1 (d), 47.0 (t), 40.7 (t), 38.5 (d), 34.9 (d), 24.4 (t). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.87; H, 6.77.

1-Ethoxycarbonyltricyclo[3.3.0.0^{2,8}]octan-3-one ethylene ketal (**241**). A mixture of **173** (2000 mg, 10.3 mmol), anhydrous ethylene glycol (1.72 mL, 30.9 mmol), PPTS (170 mg, catalyst) and benzene (20 mL) was refluxed overnight in a flask equipped with a Dean-Stark tube. After 12 hours the reaction mixture was poured into cold water and extracted with ether. The ether extract was dried, rotovaped and chromatographed to yield **241** (2203 mg, 90%) as a colorless oil and a small amount of unreacted **173** (148 mg) was recovered. Rf (1:1 ether/hexane) 0.44. IR (KBr) 1720; ^{1}H NMR δ 4.11 (q, J=7 Hz, 2H), 4.00-3.85 (m, 4H), 3.18-3.13 (m, 1H), 2.53-2.45 (m, 1H), 2.33-1.95 (m, 5H), 1.63 (d, J=14 Hz, 1H),1.60-1.54 (m, 1H), 1.24 (t, J=7 Hz, 3H); ^{13}C NMR δ 173.1 (s), 117.5 (s), 64.7 (t), 63.8 (t), 60.2 (t), 48.2 (t), 48.2 (s), 45.0 (d), 40.6 (d), 40.4 (t), 37.7 (d), 23.6 (t), 14.1 (q). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.38; H, 7.68.

Tricyclic diol **244**. Tricyclic ethyl ester **241** (2000 mg, 8.40 mmol) was dissolved in CH_2Cl_2 (16 mL) and chilled to -78°C. To this solution was dropwise added DIBAH (1.0 M in hexane, 33.6 mL, 33.6 mmol) through a syringe. The reaction was warmed up to room temperature and stirrer for 12 hours. Chilled to 0°C, the reaction was quenched with water. The aqueous solution of Rochelle's salt was added and stirred vigorously till the two-layer separation line was clear. The mixture was multiply extracted with ethyl acetate. The acetate extract was dried,

rotovaped and chromatographed to give diol **244** (1176 mg, 71%) as a thick oil. Rf (ether) 0.15; Rf (ethyl acetate) 0.25. IR (KBr) 3356, 2937, 2860, 1104, 1068, 1018; ^{1}H NMR δ 4.51 (m, 1H), 3.79-3.43 (m, 6H), 3.11 (s, 1H), 2.96 (s, 1H), 2.63 (m, 1H), 2.51-2.40 (m, 1H), 2.30-2.20 (m, 1H), 2.12-1.99 (m, 1H), 1.96-1.86 (m, 1H), 1.62-1.51 (m, 3H), 1.39 (d, J=14 Hz, 1H); ^{13}C NMR δ 83.7 (d), 70.0 (t), 65.3 (t), 61.8 (t), 50.4 (s), 44.5 (d), 44.3 (t), 39.8 (t), 35.0 (d), 32.5 (d), 24.6 (t). HRMS for $C_{11}H_{18}O_3$ M+H, calcd: 199.1334. Found: 199.1380.

1-Hydroxymethyltricyclo[3.3.0.0^{2,8}]octan-3-one ethylene ketal (**242**). Ethyl ester **241** (3210 mg, 13.5 mmol) was dissolved in CH_2Cl_2 (25 mL) and chilled to -78°C. To this solution was dropwise added DIBAH (1.0 M in hexane, 28.3 mL, 28.3 mmol) through a syringe. After 1 hour, the reaction was quenched with ethanol, and diluted with a large amount of ethyl acetate. The aqueous solution of Rochelle's salt was added and the mixture was vigorously stirred to clear up the aqueous phase. The mixture was multiply extracted with ethyl acetate. The organic extract was dried, rotovaped and chromatographed to give **242** (2530 mg, 96%) as a colorless oil. Rf (ether): 0.36. IR (KBr) 3406; ^{1}H NMR δ 4.01-3.66 (m, 6H), 3.34-3.30 (m, 1H), 2.71-2.67 (m, 1H), 2.18-1.88 (m, 3H), 1.59 (d, J=14 Hz, 1H), 1.57-1.47 (m, 3H); ^{13}C NMR δ 119.0 (s), 64.6 (t), 64.5 (t), 63.4 (t), 49.0 (s), 48.5 (t), 42.7 (d), 40.0 (t), 38.6 (d), 30.0 (d), 23.9 (t). HRMS for $C_{11}H_{16}O_3$ M+H, calcd: 197.1178. Found: 197.1226.

Oxidation of tricyclic alcohol **242** using PCC. Tricyclic alcohol **242** (280 mg, 1.43 mmol) was dissolved in CH_2Cl_2 (1.5 mL). PCC (618 mg, 2.86 mmol) and silica gel (618 mg) were finely ground in a mortar. This mixture was suspended in CH_2Cl_2 (6 mL). This suspension was added to the stirred **242** solution. The oxidation was complete in 1.5 hour. The dark reaction mixture was diluted with ether and filtered through a celite bed in a Büchner funnel. The bed was rinsed with copious amount of ether. The ether solution was rotovaped and

chromatographed to give 1-formyltricyclo[3.3.0.0^{2,8}]octane-3-one **240** (144 mg, 67%), Rf (ether) 0.57; and **243** (10 mg, 4%), Rf (ether): 0.36.

1-Formyltricyclo[3.3.0.0^{2,8}]octan-3-one ethylene ketal (**243**). Primary alcohol **242** (2050 mg, 10.5 mmol) was dissolved in CH_2Cl_2 (20 mL). To this solution, celite (4.0 g) and PDC (7866 mg, 21.0 mmol) were added. The reaction mixture was stirred overnight. It was diluted with a large amount of ether and vigorously stirred for 20 minutes. The ether solution was decanted and a new portion of ether was added to the mud. This process was repeated 5 times. The ether solutions decanted were combined, rotovaped and chromatographed to give **243** (1368 mg, 67%) as an oil. Rf (2:1 ether/hexane) 0.45. ^{1}H NMR δ 9.09 (s, 1H), 4.03-3.85 (m, 4H), 3.25-3.20 (m, 1H), 2.50-2.23 (m, 4H), 2.13-1.99 (m, 2H), 1.69 (d, J=15 Hz, 1H), 1.66-1.59 (m, 1H); ^{13}C NMR δ 198.0 (d), 116.9 (s), 64.8 (t), 63.9 (t), 59.6 (s), 48.3 (t), 45.3 (d), 40.5 (t), 37.9 (d), 37.6 (d), 23.3 (t). HRMS for $C_{11}H_{14}O_3$, calcd: 194.0943. Found: 194.0958.

1-(1-Hydroxy-3-butenyl)tricyclo[3.3.0.0^{2,8}]octan-3-one (**239**). Aldehyde **243** (480 mg, 2.47 mmol) was dissolved in THF (12 mL) and chilled to -78°C. To the solution was dropwise added allylmagnesium bromide (1.0 M in ether, 9.9 mL, 9.9 mmol) through a syringe. After 1 hour, the dry ice bath was removed. After stirring for another hour, the reaction was quenched with ethanol and acidified by 3 M HCl. After stirring for 30 minutes, the mixture was extracted with ethyl acetate. The acetate phase was dried, rotovaped and chromatographed to give **239** (403 mg, 85%) as an oil. The GC ratio of the two diastereomers of **239** was 1.3:1. Rf (ether) 0.50. IR (KBr) 3419, 1709; ^{1}H NMR δ 5.93-5.78 (m, 1H), 5.20-5.10 (m, 2H), 3.84-3.70 (m, 1H), 3.00-2.93 (m, 1H), 2.82 (s, broad, 1H), 2.64-2.52 (m, 1H), 2.45-2.25 (m, 2H), 2.16-2.00 (m, 4H), 1.80-1.74 (1H: 1.77, d, J=18 Hz, 0.43 H; 1.76, d, J=18 Hz, 0.57 H), 1.69-1.53 (m, 2H); ^{13}C NMR δ 215.5 (s), 134.5 (d), 117.8 (t), 71.2 (d), 55.2 (s), 47.3 (t), 43.2 (d), 40.2 (t), 40.0

(t), 38.3 (d), 34.3 (d), 25.1 (t) for the major diastereomer and δ 215.3 (s), 134.3 (d), 117.9 (t), 70.9 (d), 54.8 (s), 47.1 (t), 42.7 (d), 40.0 (t), 39.8 (t), 38.2 (d), 34.6 (d), 25.1 (t) for the minor diastereomer. HRMS for $C_{12}H_{16}O_2$ M+H, calcd: 193.1229. Found: 193.1226.

11-Hydroxy-9-methyltricyclo[6.3.0.0^{1,5}]undecan-3-one (**245**). Compound **239** (120 mg, 0.625 mmol) was dissolved in benzene (6.2 mL). To the solution was added TBTH (336 mL, 1.25 mmol) and AIBN (102 mg, 0.625 mmol). The mixture was degassed with argon for 15 minutes and refluxed overnight. After 14 hours, ethanol was added to quench the reaction. The mixture was rotovaped and chromatographed to yield cyclization product **245** (113 mg, 94%) as an oil. The GC ratio of the major (endo-C9-methyl) and the minor (exo-C9-methyl) cyclization products was 57:1. The GC ratio of the two C11 diastereomers of the endo-C9-methyl products was still 1.3:1. The major and minor cyclization products had same Rf and they were not separable from each other. Rf (ether) 0.56. IR (KBr) 3432, 1727; ^{1}H NMR δ 3.98-3.82 (m, 1H), 3.02-2.90 (m, 1H), 2.73-2.40 (m, 3H), 2.27-2.00 (m, 3H), 1.96-1.20 (m, 6H), 0.97-0.92 (3H: 0.96, d, J=7 Hz; 0.93, d, J=7 Hz); ^{13}C NMR δ 221.2 (s), 81.2 (d), 59.6 (s), 55.2 (d), 51.3 (t), 44.0 (t), 41.8 (d), 40.2 (t), 34.0 (t), 31.0 (d), 27.9 (t), 14.5 (q) for the major C11 diastereomer and δ 220.7 (s), 77.3 (d), 63.0 (s), 54.9 (d), 46.7 (d), 44.9 (t), 43.1 (t), 41.9 (t), 34.0 (t), 33.2 (d), 27.0 (t), 14.6 (q) for the minor C11 diastereomer. HRMS for $C_{12}H_{18}O_2$ M+H, calcd: 195.1385. Found: 195.1383.

11-Oxo-9-methyltricyclo[6.3.0.0^{1,5}]undecan-3-one (**249**). Triquinane alcohol **245** (31 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (0.5 mL). PCC (70 mg, 0.32 mmol) and silica gel (70 mg) were finely ground and added to the **245** solution. After stirring for 1 hour, a large amount of ether was added and the dark brown suspension was filtered through a celite bed in a Büchner. The bed was thoroughly rinsed with ether. The ether phase was rotovaped and

chromatographed to give the oxidation product **249** (24 mg, 78%) as an oil. Rf (2:1 ether/hexane) 0.47. IR (KBr) 1728; ^{1}H NMR δ 2.70-2.66 (m, 1H), 2.64-2.58 (m, 2H), 2.46-2.04 (m, 6H), 1.93-1.83 (m, 1H), 1.56-1.45 (m, 1H), 1.39-1.21 (m, 2H), 1.14 (d, J=6 Hz, 3H); ^{13}C NMR δ 222.1 (s), 216.5 (s), 64.4 (s), 54.4 (d), 46.6 (t), 45.6 (d), 43.8 (t), 43.0 (t), 34.8 (t), 30.1 (d), 26.9 (t), 16.2 (q). HRMS for $C_{12}H_{16}O_2$, calcd: 192.1150. Found: 192.1159.

1,5-Dimethylbicyclo[2.2.0]octane-3,7-dione (**250**).[78] This synthetic work was identical to that described by Weiss and co-workers.[78] A buffer solution (pH 8.3) was prepared with $NaHCO_3$ (5.6 g) and water (400 mL). In an Erlenmeyer flask, dimethyl ketomalonate **253** (24.3 g, 140 mmol) was mixed with the buffer solution (70 mL). To this rapidly stirred mixture, 2,3-butadione **254** (6.0 g, 70 mmol) was added. The mixture was stirred 18 hours and a yellow suspension was obtained. Solid **255** was collected by a Büchner funnel and washed with water until the solid was white in color. HRMS for $C_{18}H_{22}O_{10}$, calcd: 398.1213. Found: 398.1172. White solid **255** was then dissolved in 1 M HCl (200 mL) and glacial acetic acid (39 mL). The mixture was vigorously stirred and refluxed for 8 hours. After chilled in an ice bath, the mixture was multiply extracted with chloroform. The chloroform extracts were combined and washed with water and $NaHCO_3$ (aq.) until the aqueous layer neutral in pH. The chloroform solution then was dried and rotovaped to afford **250** (10.2 g, 88%) as a white solid. Rf (ether) 0.45. ^{1}H NMR δ 2.41 (d, J=18 Hz, 4H), 2.34 (d, J=18 Hz, 4H), 1.23 (s, 6H); ^{13}C NMR δ 215.9 (2C, s), 50.7 (4C, t), 45.2 (2C, s), 21.7 (2C, q). HRMS for $C_{10}H_{14}O_2$, calcd: 166.0994. Found: 166.0990. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.13; H, 8.44.

2-Bromo-1,5-dimethylbicyclo[2.2.0]octane-3,7-dione (**251**).[80] This synthetic work was identical to that described by Gleiter and co-workers.[80] A solution of dione **250** (2.0 g, 12.1 mmol) in chloroform (20 mL) and ethyl acetate (20 mL)

was refluxed for 30 minutes in a 3-necked flask. To the refluxed mixture, anhydrous $CuBr_2$ powder (3.8 g, 16.9 mmol) was added in small portions in more than 4 hours. A new small portion of the dark green $CuBr_2$ was added only after the previously added $CuBr_2$ had totally turned yellow in color. After the completion of $CuBr_2$ addition, the reaction mixture was refluxed overnight. A mixture of yellow solid and orange solution was then obtained. The yellow solid was removed with a Büchner funnel and the orange organic filtrate was washed with water and $NaHCO_3$ (aq.). The organic solution then was dried, rotovaped and chromatographed. The bromination product **251** (1.35g, 46%) was isolated as a white crystal. Rf (ether) 0.52. ^1H NMR δ 4.58 (s, 1H), 2.57-2.26 (m, 6H), 1.42 (s, 3H), 1.32 (d, J=0.9 Hz, 3H). HRMS for $C_{10}H_{13}O_2Br$, calcd: 244.0099. Found: 244.0029.

1,5-Dimethyltricyclo[3.3.0.0^{2,8}]octane-3,7-dione (**252**).[80] This synthetic work was identical to that described by Gleiter and co-workers.[80] A solution of DBU (871 μL, 5.84 mmol) in anhydrous acetonitrile (3.0 mL) was added dropwise to the stirred solution of bromodiketone **251** (1300 mg, 5.31 mmol) in anhydrous acetonitrile (13.3 mL). The mixture was stirred overnight at room temperature. The reaction mixture then was rotovaped and pumped to remove acetonitrile. The residue was dissolved in chloroform and was washed with water, 1M HCl, and $NaHCO_3$ (aq.). The orange chloroform phase was decolorized with charcoal and dried with $MgSO_4$. The chloroform phase then was rotovaped and the residue was chromatographed. The desired product **252** was isolated as a white crystal (628 mg, 72%). Rf (ether) 0.39. ^1H NMR δ 2.56 (d, J=17 Hz, 2H), 2.36 (s, 2H), 2.16 (d, J=17 Hz, 2H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR δ 208.3 (2C, s), 56.2 (2C, t), 47.5 (2C, d), 41.8 (2C, s), 22.8 (q), 13.6 (q). Anal. Calcd for $C_{10}H_{14}O_2$: C, 73.15; H, 7.37. Found: C, 72.98; H, 7.32.

Preparation of **252** using Barluenga's iodination method.[81] To the solution of dione **250** (1000 mg, 6.02 mmol) and white crystal $HgCl_2$ (820 mg, 3.01 mmol) in CH_2Cl_2 (12 mL) was added iodine (1530 mg, 6.02 mmol). $HgCl_2$ was not soluble in CH_2Cl_2 and the reaction mixture turned into dark purple after the iodine addition. A dark orange powder (HgI_2) gradually formed and accumulated in amount. After stirring for 6 hours, the insoluble HgI_2 was removed by a Büchner filtration. The CH_2Cl_2 solution then was washed with 0.5 M $Na_2S_2O_3$ and saturated KI aqueous solutions. The organic phase was dried and rotovaped to give **256** (1.43 g) as a crude light brown solid. The solid was dissolved in acetonitrile (13 mL). To this stirred solution was dropwise added DBU (880 μL, 5.90 mmol, in 3 mL acetonitrile) through an additional funnel. The mixture was stirred overnight and then was rotovaped. The residue was dissolved in $CHCl_3$. The solution was washed by water, 1 M HCl and saturated $NaHCO_3$ (aq.). The organic phase then was dried, rotovaped and the residue was chromatographed to afford **252** (508 mg, 51%) as a white needle crystal. Rf (ether) 0.39.

Preparation of **252** using Horiuchi's iodination method.[82] A dark purple mixture of dione **250** (3000 mg, 18.1 mmol), iodine (5.05 g, 19.9 mmol) and $Cu(OAc)_2 \cdot H_2O$ (4.35 g, 21.7 mmol) in glacial acetic acid (450 mL) was stirred overnight at 60°C in a flask equipped with a condenser. A green solution with white precipitate CuI formed. The white precipitate was removed by simple filtration and the filtrate was poured into 400 mL water. The mixture was extracted with ether. The ether extract was washed with water and saturated $NaHCO_3$ (aq.) to remove acetic acid. The ether phase was rotovaped to give a dark red oil. It was dissolved in $CHCl_3$ and multiply washed with water and saturated $NaHCO_3$ (aq.) until the aqueous layer not acidic. The $CHCl_3$ phase was dried and rotovaped to afford a crude orange oil. It was dissolved in

acetonitrile (40 mL). To this solution was added DBU (3.5 mL, 23.3 mmol, in 12 mL acetonitrile) dropwise. The reaction mixture was stirred overnight and then rotovaped. The residue was dissolved in $CHCl_3$. The solution was washed with water, 1 M HCl and saturated $NaHCO_3$ (aq.). The organic phase was dried, rotovaped and chromatographed to give **252** (678 mg, 25%) as white needle crystal. Rf (ether) 0.39.

7-(3-Butenyl)-1,5-dimethyl-7-hydroxyltricyclo[3.3.0.0^{2,8}]octan-3-one (**238**). The dione **252** (280 mg, 1.71 mmol) was dissolved in THF (5.7 mL) and chilled to -78°C. To the stirred solution was dropwise added 3-butenylmagnesium bromide (0.5M in THF, 4.44 mL, 2.22 mmol) through a syringe in 10 minutes. The reaction was quenched in 3 hours with water, acidified with 1 M HCl and extracted with ethyl acetate. The acetate extract was dried, rotovaped and chromatographed. Unreacted starting dione **252** (46 mg) was recovered and **238** (188 mg, 64%) was isolated as a white solid. The GC ratio for the Grignard addition stereoselectivity was found higher than 100:1. Rf (ether) 0.55. ^{1}H NMR δ 5.82 (m, 1H), 4.95 (m, 2H), 3.42 (s, 1H), 2.40-2.08 (m, 4H), 2.00-1.67 (m, 6H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR δ 214.9 (s), 138.6 (d), 114.4 (t), 80.3 (s), 58.5 (t), 54.8 (t), 50.4 (d), 49.5 (s), 46.3 (s), 45.7 (d), 42.3 (t), 28.7 (t), 23.0 (q), 14.8 (q). HRMS for $C_{14}H_{20}O_2$ M+H, calcd: 221.1542. Found: 221.1544. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.31; H, 9.16.

Linear triquinane **259**. Tricyclic ketone **238** (34 mg, 0.155 mmol), TBTH (125 mL, 0.465 mmol) and AIBN (25 mg, 0.155 mg) were dissolved in benzene (0.6 mL). The mixture was degassed with steady argon stream for 15 minutes and refluxed overnight. The reaction was quenched with ethanol and chromatographed to afford **259** (28 mg, 83%) as an oil. The GC ratio for the endo-C9-methyl selectivity was higher than 4:1. Rf (ether) 0.68. IR 4000 (broad), 2956, 1708, 1462; ^{1}H NMR δ 2.35 (q, J=18 Hz, 1H), 1.97-1.85 (m, 2H), 1.73-

1.66 (m, 2H), 1.53-1.24 (m, 9H), 0.91-0.78 (m, 6H); ^{13}C NMR δ 214.1 (s), 81.0 (s), 58.9 (s), 55.0 (t), 50.0 (d), 46.5 (s), 46.0 (d), 43.1 (t), 29.3 (t), 27.4 (t), 23.2 (q), 15.0 (q), 13.7 (q), 8.8 (t). HRMS for $C_{14}H_{22}O_2$, calcd: 222.1620. Found: 222.1616. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; Found: C, 75.62; H, 9.95.

Aldol reaction product **263E/T**. A mixture of cyclopropyl ketone **137** (200 mg, 1.14 mmol), TBTH (458 μL, 1.71 mmol) and AIBN (56 mg, 0.34 mmol) in benzene (5 mL) was degassed with argon for 15 minutes. The mixture was refluxed for 2 hours and cooled to room temperature. Benzaldehyde **262** (346 μL, 3.41 mmol) then was added. The mixture was stirred overnight. The mixture then was rotovaped and chromatographed to give diastereomic mixture **263E/T** (312 mg, 97%) as a thick oil. The ratio of erythro **263E** to threo **263T** was 4.4:1 by proton NMR integration. Rf (1:1 ether/hexane) 0.24. For erythro **263E**, ^1H NMR δ 7.89 (d, J=9 Hz, 2H), 7.44-7.17 (m, 5H), 6.90 (d, J=9 Hz, 2H), 5.05 (d, J=4.5 Hz, 1H), 3.84 (s, 3H), 3.67 (m, 1H), 2.58 (s, 1H), 1.43-1.31 (m, 2H), 0.76 (t, J=7 Hz, 3H); ^{13}C NMR δ 203.7, 163.8, 142.1, 130.6 (2C), 130.0, 128.1 (2C), 127.2, 126.1 (2C), 113.8 (2C), 73.8, 55.4, 53.5, 20.4, 12.1. For threo **263T**, ^1H NMR δ 4.99 for the carbinol proton (d, J=5.9 Hz); ^{13}C NMR δ 75.6 for the carbinol. HRMS for $C_{18}H_{20}O_3$ M+H, calcd: 285.1491. Found: 285.1463.

Aldol reaction product **265**. A mixture of cyclopropyl ketone **137** (200 mg, 1.14 mmol), TBTH (458 μL, 1.71 mmol) and AIBN (56 mg, 0.34 mmol) in benzene (4 mL) was degassed with argon for 15 minutes. The mixture was refluxed for 2 hours and cooled to room temperature. Cyclohexanecarboxaldehyde **264** (412 μL, 3.41 mmol) then was added. The mixture was stirred for 18 hours. The mixture then was rotovaped and chromatographed to give diastereomic mixture **265** (303 mg, 92%) as a thick oil. The ratio of the major diastereomer to the minor ones was 46:1 by GC. Rf (1:1 ether/hexane) 0.36. For the major

diastereomer, ^{1}H NMR δ 7.96 (d, J=9 Hz, 2H), 6.96 (d, J=9 Hz, 2H), 3.87 (s, 3H), 3.65-3.55 (m, 2H), 2.02-1.87 (m, 2H), 1.82-1.66 (m, 4H), 1.53-0.84 (m, 11H); ^{13}C NMR δ 204.1 (s),163.7 (s), 130.6 (d, 2C), 130.3 (s), 113.8 (d, 2C), 76.0 (d), 55.3 (d), 48.0 (d), 40.6 (d), 29.4 (t), 28.8 (t), 26.2 (t), 26.0 (t), 25.8 (t), 19.7 (t), 12.3 (q). HRMS for $C_{18}H_{26}O_3$, calcd: 290.1882. Found: 290.1814.

Alkylation reaction product **267**. A mixture of ketone **137** (200 mg, 1.14 mmol), TBTH (458 μL, 1.71 mmol) and AIBN (56 mg, 0.34 mmol) in benzene (4 mL) was degassed with argon for 15 minutes. The mixture was refluxed for 2 hours and cooled to room temperature. HMPA (987 μL, 5.68 mmol) was added and the mixture was stirred for 5 minutes. Allyl bromide (393 μL, 4.54 mmol) was added and the mixture was refluxed for 24 hours. A DBU workup procedure was used to remove excess TBTH and other tin byproducts.[34d,93] The reaction mixture was diluted with ether. Following addition of DBU (305 μL, 2.04 mmol) and 2-3 drops of water, an ethereal solution of iodine was added dropwise until the iodine orange color persisted. Rapid suction filtration through silica gel bed was performed. The silica gel bed was rinsed with ether, and the solution was concentrated and subjected to flash column chromatography to afford **267** (212 mg, 86%) as a thick oil. Rf (1:1 ether/hexane) 0.72. ^{1}H NMR δ 7.95 (d, J=9 Hz, 2H), 6.94 (d, J=7 Hz, 2H), 5.75 (m, 1H), 5.05-4.94 (m, 2H), 3.86 (s, 3H), 3.41 (m, 1H), 2.38 (m, 2H), 1.69 (m, 2H), 0.87 (t, J=7 Hz, 3H); ^{13}C NMR δ 202.0, 163.3, 136.0, 130.4 (3C), 116.3, 113.7 (2C), 55.3, 46.8, 36.0, 25.0, 11.6. HRMS for $C_{14}H_{18}O_2$, calcd: 218.1307. Found: 218.1304. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; Found: C, 76.92; H, 8.37.

Alkylation reaction product **268**. A mixture of ketone **137** (200 mg, 1.14 mmol), TBTH (458 μL, 1.71 mmol) and AIBN (56 mg, 0.34 mmol) in benzene (2 mL) was degassed with argon for 15 minutes. The mixture was refluxed for 2 hours and cooled to room temperature. HMPA (987 μL, 5.68 mmol) was added and

the mixture was stirred for 3 minutes. 1-Iododecane (969 μL, 4.54 mmol) was added and the mixture was refluxed for 18 hours. The mixture was directly subjected on flash column chromatography to give **268** (342 mg, 95%) as a thick oil. Rf (1:1 ether/hexane) 0.87. ^{1}H NMR δ 7.87 (d, J=9 Hz, 2H), 6.84 (d, J=9 Hz, 2H), 3.75 (s, 3H), 3.22 (m, 1H), 1.66 (m, 2H), 1.52-1.35 (m, 2H), 1.13 (m, 16H), 0.79-0.74 (m, 6H); ^{13}C NMR δ 202.9, 163.2, 130.8, 130.3 (2C), 113.5 (2C), 55.2, 47.1, 32.1, 31.8, 29.8, 29.5 (2C), 29.4, 29.2, 27.5, 25.5, 22.6, 14.0, 11.8. HRMS for $C_{21}H_{34}O_2$, calcd: 318.2559. Found: 318.2554.

1-(4-Methoxyphenyl)hept-6-enone (**286**). A mixture of ketone **137** (200 mg, 1.14 mmol), allyltributyltin (1760 μL, 5.68 mmol) and AIBN (186 mg, 1.14 mmol) in benzene (0.5 mL) was degassed with argon for 10 minutes and heated at 80°C for 1 day. Then AIBN (186 mg, 1.14 mmol) was added and the mixture was degassed at room temperature for 10 minutes. The mixture was again heated at 80°C for 1 day. The mixture was directly subjected to column chromatography to give unreacted **137** (105 mg) and **286** (59 mg, 24%; 50% if corrected with recovered **137**). Rf (1:3 ether/hexane) 0.47. ^{1}H NMR δ 7.94 (d, J=9 Hz, 2H), 6.93 (d, J=9 Hz, 2H), 5.82 (m, 1H), 5.05-4.94 (m, 2H), 3.87 (s, 3H), 2.91 (q, J=7.5 Hz, 2H), 2.10 (q, J=7 Hz, 2H), 1.75 (m, 2H), 1.48 (m, 2H); ^{13}C NMR δ 198.9, 163.3, 138.5, 130.3 (2C), 130.1, 114.5, 113.6 (2C), 55.4, 38.0, 33.6, 28.6, 24.0. HRMS for $C_{14}H_{18}O_2$, calcd: 218.1307. Found: 218.1304.

8-Allyl-8-ethoxycarbonylbicyclo[3.2.1]octan-3-one (**287**). A mixture of tricyclic ketone **171** (330 mg, 1.70 mmol), allyltributyltin (1318 μL, 4.25 mmol) and AIBN (139 mg, 0.851 mmol) in benzene (1.7 mL) was degassed with argon for 15 minutes and refluxed for 16 hours. The mixture was directly chromatographed to give the allylation product **287** (376 mg, 94%) as a clear oil. Rf (1:1 ether/hexane) 0.58. IR (KBr) 1720; ^{1}H NMR δ 5.70-5.57 (m, 1H), 4.99-4.97 (m, 1H), 4.97-4.91 (m, 1H), 4.09 (q, J=7 Hz, 2H), 2.65 (d, J=15 Hz, 2H), 2.37 (dd,

J=4.2 Hz, 2.7 Hz, 2H), 2.25 (d, J=7 Hz, 2H), 2.13 (m, 2H), 1.91-1.87 (m, 2H), 1.44 (m, 2H), 1.17 (t, J=7 Hz, 3H); ^{13}C NMR δ 212.0 (s), 173.8 (s), 133.0 (d), 118.0 (t), 60.4 (t), 58.5 (s), 47.6 (t, 2C), 39.3 (d, 2C), 27.2 (t, 3C), 14.3 (q). HRMS for $C_{14}H_{20}O_3$ M+H, calcd: 237.1491. Found: 237.1498.

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BIOGRAPHICAL SKETCH

Zhaozhong Jon Jia was born in Kaifeng, Henan, China on October 22, 1968. As a quiet boy, he spent his early years reading books, learning painting, and playing with his cats and chickens. At high school he fell in love with chemistry under the strong influence of a great chemistry teacher Mr. Shugeng Luo. In September 1985, he left his hometown for Tianjin, a northern city 600 miles away, to study chemistry at Nankai University.

At college, organic chemistry was his obvious favorite. He dreamed that someday he could earn a Ph.D. degree in this field and devote his life to synthesizing valuable organic compounds. In his junior year, the department assigned him into the inorganic division and blocked his opportunity for further organic chemistry studies. In his final semester at Nankai, he entered Professor Daizheng Liao's lab to prepare and study Cu(II)-Fe(III) binuclear coordination compounds for his senior research. There for the first time he experienced real synthesis. In July 1989, he received his BS degree in inorganic chemistry.

Attracted by its numerous high technology research programs and beautiful suburban location, he accepted a job offer from China Institute of Atomic Energy in Beijing. His job was to study the liquid sodium purification technology to support his country's sodium-cooled fast breeder nuclear reactor program. He and his colleagues accomplished establishment of a new sodium purification loop and production of "nuclear-grade pure" sodium in 1991. They shared an research award from China's Nuclear Industries Ministry for the work.

To pursue a Ph.D. degree, he arrived at the University of Florida in August 1992. Eager to come back to organic chemistry, he joined Professor Eric Enholm's group in the October. His research efforts focused on the synthetic applications of ketyl radicals, generated by the reaction of a carbonyl functionality with tributyltin hydride or samarium diiodide. After his hard-working struggles in the initial one-and-a-half year with a couple of fruitless projects, he gradually grew up and realized that real chemistry is much more challenging than a written reaction or synthetic route on paper. With progress in this cyclopropane fragmentation project, he became a Ph.D. candidate in January 1995, and presented his research in the national ACS meeting in March 1996 in New Orleans. In December 1996, he obtained his Ph.D. degree in organic chemistry at the University of Florida in Gainesville, Florida.

In January 1997, he joined Professor Bert Fraser-Reid's group as a postdoctoral research associate at the Natural Products and Glycotechnology Research Institute in Durham, North Carolina.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eric J. Enholm, Chairman
Associate Professor of Chemistry

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Merle A. Battiste
Professor of Chemistry

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William R. Dolbier, Jr.
Professor of Chemistry

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James M. Boncella
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Margaret O. James
Professor of Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1996

Dean, Graduate School